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’

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 Force Fertility Preservation in Severe Disease in collaboration with the “US OncoFertility Consortium”
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- Perspectives for a European network for fertility preservation - **Michael von Wolff (Switzerland)**  
  
- Management strategies for oncology consults and collaboration - **Jacqueline Jeruss (USA)**  
  
- Management strategies for centralised cryobanks and the European directive - **Markus Montag (Germany)**  
  
- Clinical management: fertility risks by diagnosis - What cancer requires immediate intervention - **Dror Meirow (Israel)**  
  
- Addressing the specific needs of young children with cancer - **Hamish Wallace (United Kingdom)**  
  
- Where research becomes treatment: ethical issues - **Françoise Shenfield (United Kingdom)**  
  
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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).

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
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

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<td>Anna Veiga</td>
<td>Spain</td>
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<td>Jop Geraedts</td>
<td>Netherlands</td>
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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 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

ESHRE Membership (1/3)

TOTAL MEMBERSHIP*: 5 659 members

* as of July 2010
ESHRE Membership (2/3)

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</tr>
<tr>
<td>Student Member**</td>
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*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/Paramedics € 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
- Psychology & Counselling
- Early Pregnancy
- Reproductive Genetics
- Embryology
- Reproductive Surgery
- Endometriosis / Endometrium
- Stem Cells
- Ethics & Law
- Reproductive Endocrinology
- Safety & Quality in ART
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: 8,095 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)
- **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)

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**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
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

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

Preservation of Fertility After Cancer
Life preserving treatments
- Chemotherapy
- Radiation
- Surgery
Can threaten fertility
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.

Who is at risk?

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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).

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Probability of Menopause

- Probability of Menopause

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Probability of Menopause

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<td>75</td>
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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 mutations that lead to loss of fertility and early menopause (e.g. Turner's Syndrome, Fragile X Carriers)
- Individuals who carry a mutation that predisposes an individual to certain types of cancer and anticipated treatment-induced risk of infertility

Hirschfield, Gracia and Woodruff, submitted

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

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 I had ovarian failure. You know it was...it was traumatic..."

"...my first reaction was had this been offered when I was 14, I would have been like yes, yes, just do it. But my mother, my parents probably, would have been although we'll 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
The Mission of the Oncofertility Consortium

To focus on the fertility threat posed 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
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-Engelstein, L JCO, 2010
Gardino et al., JARG, 2010

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, California, Rev. 50
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/

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
Virtual Grand Rounds -GLOBAL

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
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
Our goal is to build the program as a global team and in so doing...
...expand options for the reproductive future of cancer survivors.

Support

The work presented in this talk was supported by the SCOPHR Center for Reproductive Research, NICHD U54 HD041897; 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.
Thank you!

References and Resources


For more information:

- SaveMyFertility.org
- Oncofertility Consortium: www.myoncofertility.org, www.oncofertility.northwestern.edu or call 1-866-708-FERT (1-866-3378)
- Find-an-Endocrinologist: www.hormone.org/FindAnEndo/index.cfm
- Fertile Hope: www.fertilehope.org
- Sharing Hope Program: http://www.fertilehope.org/financial-assistance/index.cfm
- American Society for Reproductive Medicine: www.asrm.org/patient_resources
- American Society of Clinical Oncology
- Cancer Information: www.cancer.net
- RESOLVE: The National Infertility Association: www.resolve.org
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

Michael von Wolff, MD

University Women’s Hospital
Department of Gynecological Endocrinology and Reproductive Medicine
**IVF – Data collection in Europe**

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

20 countries, 359,000 cycles in a population of 422 million.

**Fertility preservation in Europe – Legal restrictions**

For example:

<table>
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<th>Country</th>
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<td>Yes</td>
<td>partially</td>
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**Fertility Preservation techniques and success rates**

Estimated birth rates following fertility preservation:

- Cryopreservation of tissue: max. 20% ??? (von Wolff et al., 2009; Dosman et al., 2011)
- Cryopreservation of unfertilized oocytes: ~ 50% lower than after cryo of fertilized oocytes (Auer et al., 2011)
- Cryopreservation of fertilized oocytes: 25%-35% (18-25y) 40% (35-40y) ? (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

(Claweins 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 & Blaser, 2009
- GnRHa: BlumerHild 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 questionnaire 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:

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### 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 Republic
- Netherlands
- 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:**

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Survey – National / Large local programmes - men?

"Established" national programmes / Large local programmes:

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Survey – National / Large local programmes - women?

"Established" programmes with centralized registries (2010):

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National networks

Centralized: Few specialised national medical centers, i.e. Denmark
Decentralized: Many specialised medical centers with a central coordinating body, i.e. Germany
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

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

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


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

Cancer diagnosis

Is the patient interested in future fertility?

Yes

Refer to patient navigator for counseling and multidisciplinary coordination of care

Male patients:
- Fertility-sparing treatment modification
- Sperm cryopreservation
- Electroejaculation
- Surgical sperm extraction

Female patients:
- Fertility-sparing treatment modification
- IVF/embryo cryopreservation
- Oophoropexy for radiation shielding
- Oocyte cryopreservation
- Ovarian tissue cryopreservation

Initiation of therapy

*Experimental

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

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
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 live births

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
  - IVF/ET: 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

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
**WOMEN**

**CANCER DIAGNOSIS**
- Choose fertility preservation before cancer treatment:
  - Yes
  - No

1st Decision Point
- General surgery needed to support medical and emotional health
- Sperm retrieval
- Ovarian tissue cryopreservation
- Ovarian transposition
- Ovarian shielding

2nd Decision Point
- Sperm retrieval type
- No male partner available
- Donor sperm
- Adoption

3rd Decision Point
- Ovarian stimulation (OS)
- Mature oocyte retrieval
- GnRH Analog or Antagonist Treatment *
- Chemotherapy can be delayed and hormonal stimulation not contraindicated

4th Decision Point
- In-vitro maturation (IVM) of oocytes
- Male partner available, oocyte insemination
- No male partner available
- Embryo cryopreservation
- Heterotopic transplant
- Orthotopic transplant
- Attempt natural pregnancy

5th Decision Point
- Sperm cryopreservation

---

**MEN**

**CANCER DIAGNOSIS**
- Choose fertility preservation before cancer treatment:
  - Yes
  - No

1st Decision Point
- General surgery needed to support medical and emotional health
- Testicular sperm extraction
- Percutaneous sperm extraction
- Testicular suppression with Gonadotropin-releasing Hormones (GnRH) Analog or Antagonist Treatment
- Male partner available
- No male partner available

2nd Decision Point
- Sperm retrieval type
- No male partner available
- Donor sperm
- Adoption

3rd Decision Point
- Female partner available
- No female partner available

---

**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

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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

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

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
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


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 transposition 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

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.
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

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

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
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

Patients per year for centralised ovarian tissue freezing / Bonn

Patient characteristics - Cryobank Bonn -
### 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
• Responsibility 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
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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
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- 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 information 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

  - 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.

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

Ovarian Failure
Post Chemotherapy

Previous Treatments
Age
Gynecology operation
Chemotherapy Agents

Human Follicle count representing the reserve of the ovary

Wallace Kelsey 2010
Ovarian Failure by Drug Families

Age adjusted Odds ratio exposed vs. unexposed

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>Alkylating agents</th>
<th>Antibiotics</th>
<th>Anti Metabolites</th>
<th>Rest Alkyls</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>2.5</td>
<td>3</td>
<td>3.5</td>
<td>4</td>
</tr>
</tbody>
</table>

Meierow Hum Reprod 2001

American Society of Clinical Oncology

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

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Treatment</th>
<th>Ovarian failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howell &amp; Shalet Review 98</td>
<td>Aggressive treatment</td>
<td>38% - 57%</td>
</tr>
<tr>
<td>Meirow 99</td>
<td>Relapse post 1st treatment</td>
<td>32%</td>
</tr>
<tr>
<td>Bokemeyer</td>
<td>Infradiaphragmatic Rx.</td>
<td>50%</td>
</tr>
<tr>
<td>Brusamolino 2000</td>
<td>Ovarian sparing protocol</td>
<td>&lt;25y – 0%&lt;45y – 30%</td>
</tr>
</tbody>
</table>

Wallace & Meirow 2010
## Ovarian failure in breast cancer patients

<table>
<thead>
<tr>
<th>Chemo</th>
<th>Age</th>
<th>Ovarian failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>&lt; 30</td>
<td>0 %</td>
</tr>
<tr>
<td>AC</td>
<td>30-39</td>
<td>13 %</td>
</tr>
<tr>
<td>FAC</td>
<td>&lt; 30</td>
<td>0 %</td>
</tr>
<tr>
<td>FAC</td>
<td>30-39</td>
<td>10-25 %</td>
</tr>
<tr>
<td>CMF</td>
<td>&lt; 30</td>
<td>19 %</td>
</tr>
<tr>
<td>CMF</td>
<td>30-39</td>
<td>30-40 %</td>
</tr>
<tr>
<td></td>
<td>+ Taxane</td>
<td></td>
</tr>
</tbody>
</table>

[Wallace & Meirow 2010]

---

## Breast cancer - ovarian failure post treatment

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/ treatment</th>
<th>Ovarian failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower E.E 1999</td>
<td>Pre menopause</td>
<td>45%</td>
</tr>
<tr>
<td>Meirow D 1999</td>
<td>&lt;35 years</td>
<td>28%</td>
</tr>
<tr>
<td>Goodwin P. 1999</td>
<td>&lt;44 years</td>
<td>50%</td>
</tr>
<tr>
<td>Burstein H. 2000</td>
<td>CMF</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>30-39</td>
<td>20-40%</td>
</tr>
<tr>
<td></td>
<td>CAF</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>10-25%</td>
</tr>
<tr>
<td></td>
<td>30-39</td>
<td>13%</td>
</tr>
<tr>
<td>Jonat W. 2001</td>
<td>Pre menopause</td>
<td>60%</td>
</tr>
<tr>
<td>Petrek 2006</td>
<td>&lt;35</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>35-39</td>
<td>30-55%</td>
</tr>
<tr>
<td></td>
<td>&gt;39</td>
<td>&gt; 55%</td>
</tr>
</tbody>
</table>

[Petrek, J. Clin Oncol 2006]

---

## Ablative Chemotherapy & Bone Marrow Transplantation

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>% failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanders 96</td>
<td>73 mean 38</td>
<td>99</td>
</tr>
<tr>
<td>Teinturier 98</td>
<td>21 2 - 17</td>
<td>72</td>
</tr>
<tr>
<td>Thibaud 98</td>
<td>31 3.2 - 17</td>
<td>80</td>
</tr>
<tr>
<td>Meirow 99</td>
<td>63 mean 29</td>
<td>79</td>
</tr>
<tr>
<td>Grigg 2000</td>
<td>19 mean 30</td>
<td>100</td>
</tr>
</tbody>
</table>

Ovarian failure risk - very high.

[Meirow, Anderson, Wallace 2010]
Premature ovarian Failure in Childhood Cancer Survivors

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Min-max</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFC</td>
<td>Controls</td>
<td>Survivors</td>
<td>0.0042</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>5</td>
<td>1 - 34</td>
</tr>
<tr>
<td></td>
<td>8 - 12</td>
<td>0 - 12</td>
<td></td>
</tr>
<tr>
<td>AMH</td>
<td>Controls</td>
<td>Survivors</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>1.8</td>
<td>0.6</td>
<td>0.3 - 6.3</td>
</tr>
<tr>
<td></td>
<td>&lt;0.1 - 2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH</td>
<td>Controls</td>
<td>Survivors</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>8.0</td>
<td>11.6</td>
<td>3.1 - 17.7</td>
</tr>
<tr>
<td></td>
<td>3.3 - 24.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inh B</td>
<td>Controls</td>
<td>Survivors</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>46.6</td>
<td>24.3</td>
<td>10.0 - 152.1</td>
</tr>
<tr>
<td></td>
<td>10.0 - 91.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E2</td>
<td>Controls</td>
<td>Survivors</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>38.8</td>
<td>120</td>
<td>12.0 - 89.0</td>
</tr>
<tr>
<td></td>
<td>14.4 - 806.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

20 pt. in each group

2010 A. Partridge Fertil Steril

The effect of chemotherapy on growing follicles and its clinical application
IVF  > 40% of patients with Hematological malignancies had previous chemotherapy.

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

Ovarian tissue cryo-preservation post recent Chemotherapy

2-3 months post chemotherapy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age</th>
<th>IVF Eggs</th>
<th>Biopsy PMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hodgkin's D</td>
<td>21</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Hodgkin's D</td>
<td>25</td>
<td>0</td>
<td>++ ++</td>
</tr>
<tr>
<td>Hodgkin's D</td>
<td>25</td>
<td>0</td>
<td>++ ++</td>
</tr>
</tbody>
</table>

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

Meinow et al. Leukemia lymphoma 2007
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%

Waller 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
  - Pelvic Rx.
  - Alkylating agents
  - platinum agents
  - Taxanes
  - Plant alkaloids
  - Anthracyclines
  - Anti metabolites

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

- Less gonadotoxic protocols.
- Protecting agents

| Fertility preservation | OTCP | IVF | IVM | Oophoropexy |

Different approaches for fertility preservation
Currently used & experimental

- Primordial follicles
  - Early growth
  - Mature eggs
  - Stored ovarian tissue
  - Follicle maturation
  - Not practiced
  - Ovarian tissue transplantation
  - In-vitro Egg maturation
  - Mature Egg collection

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Eggs Cancer</th>
<th>2PN Cancer</th>
<th>P Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oktay 2005</td>
<td>12.3</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Knopman 2009</td>
<td>$14 \pm 9$</td>
<td>$12 \pm 7$</td>
<td>NS</td>
</tr>
<tr>
<td>Quintero 2010</td>
<td>13</td>
<td>11.5</td>
<td>7.4</td>
</tr>
<tr>
<td>Robertson 2010</td>
<td>$12 \pm 8$</td>
<td>$14 \pm 9$</td>
<td>$6 \pm 5$</td>
</tr>
<tr>
<td>Lawrenz 2011</td>
<td>$11.6 \pm 7.7$</td>
<td></td>
<td>$7$</td>
</tr>
</tbody>
</table>

Luteal Stimulation with GnRH ant

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

<table>
<thead>
<tr>
<th></th>
<th>Follicular</th>
<th>Luteal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonadotropin used</td>
<td></td>
<td>More NS</td>
</tr>
<tr>
<td>Stimulation duration</td>
<td>10.6</td>
<td>11.4</td>
</tr>
<tr>
<td>Oocytes obtained</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Fertilization rate</td>
<td>61</td>
<td>76</td>
</tr>
</tbody>
</table>

Von Wolff M et al Fertil Steril 2009

Minimal Stimulation/IVM Protocol

<table>
<thead>
<tr>
<th></th>
<th>Shalom Paz 2010</th>
<th>Maman 2010 Luteal</th>
<th>Maman 2010 follicular</th>
<th>Strowitzki 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. cycles</td>
<td>31</td>
<td>5</td>
<td>13</td>
<td>215</td>
</tr>
<tr>
<td>Oocytes/ cycle</td>
<td>$9.7 \pm 6.4$</td>
<td>$12.8 \pm 8.4$</td>
<td>$17.3 \pm 13.5$</td>
<td>8.9</td>
</tr>
<tr>
<td>Total MII in 48h</td>
<td>$7.0 \pm 7.6$</td>
<td>$9.5 \pm 7.7$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maturation rate</td>
<td>48%</td>
<td>58%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fertilization rate</td>
<td>77.8%</td>
<td>69%</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>Embryo stored</td>
<td>$4.5 \pm 2.71$</td>
<td></td>
<td>2.8</td>
<td></td>
</tr>
</tbody>
</table>
IVM results for fertility preservation

- 215 cycles
- 1922 Oocytes
- 8.9/ cycle
- 1131 matured 64%
- 5.9/ retrieval
- 515 fertilized 29%
- 2.8/ retrieval

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

T. Strowitzki 2010

Breast cancer protocols

- Cancer cells
- Lap. Ovarian
- Good No. of eggs
- Ovarian stimulation with FSH
- Low E2
- High E2
- Neoplastic change
- Good No. of eggs

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


- 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

[Graph showing follicle count over time]

[Image of follicles from thawed 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.
Addressing the specific needs of young children with cancer

Hamish Wallace

Contribution not submitted by speaker
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

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 …)
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 (1/3) 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
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 vs 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 cryopreservation, posthumous use

A simple case (in comparison)?

A much more difficult equation

- Timing of transition from 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 cryopreserve 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 cryopreserve
- 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 specific 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 feedback
• Ideally multi-centered to avoid bias due to center 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 example.
- If there is little risk, is there “nothing to lose”?
- 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

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**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
- ………

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**References : transition from research …**


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

- 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
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
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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?
Before we can effectively counsel and educate our patients, we need to train ourselves.

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

- 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 Oncofertility Training 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 (Co-PI’s Pilot Project)
- Beth Plunkett, MD
- 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

In a Global, Interdisciplinary, Academic Environment
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, paramedics 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