Conference on fertility preservation
4 December 2014 - Paris, France
Dear participant,

A warm welcome to all attending the “Conference on fertility preservation”.

We would like to inform you that as of 28 April 2014 the name of our Foundation changed to EXCEMED - Excellence in Medical Education. The name change will not impact your registration status in this or any other Foundation event.

This transition marks an exciting point in the evolution of the Foundation. We are proud to have provided world-class education to thousands of healthcare professionals over the past four decades - as a result, the Foundation has become synonymous with delivery excellence and high-impact CME.

As we further develop our scientific and geographical presence it is important to us that our name accurately reflects the independent nature of the education we provide; EXCEMED symbolises our enduring mission to support the best possible outcomes for patients through the medical education we offer. We take pride in our complete dedication to the provision of CME - it is our sole focus and our passion.

We wish you an inspiring and successful learning experience here in Paris.

Yours sincerely,

EXCEMED
General information

Venue
This live educational conference takes place at the:
Paris Marriott Rive Gauche Hotel & Conference Center
17 Boulevard Saint-Jacques
75014 Paris

Language
The official language of this live educational conference is English.

Scientific secretariat
EXCEMED - Excellence in Medical Education
Salita di San Nicola da Tolentino, 1/b
00187 Rome, Italy
Programme Manager: Simona Pantaleoni
T: +39 06 420413 569
F: +39 06 420413 677
E-mail: info@excemed.org
Specialist Medical Advisor - Fertility: Sesh K. Sunkara
Specialist Medical Advisor - Oncology: Cristina Raimondi
EXCEMED is a Swiss Foundation with headquarters in
14, Rue du Rhône, 1204 Geneva, Switzerland

Organising secretariat
Meridiano Congress International
Via Sapri, 6 - 00185 Rome, Italy
Congress Coordinator: Titty Alvino
T +39 06 88 595 310 - F +39 06 88595 234
E-mail: c.alvino@meridiano.it

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Conference on fertility preservation

EXCEMED live educational:

Conference on fertility preservation
4 December 2014 - Paris, France

Aims
As oncology treatments improve, the right to have a child becomes important for many cancer patients. Fertility preservation is therefore an important subject for oncologists as well as for specialists in reproductive medicine; the needs of people who are about to undergo cancer treatment, or who have a history of cancer, are different. There is now a greater onus on oncologists to ensure they deliver cancer care that either takes infertility into consideration (by advocating fertility preservation options), or has minimal long-term effects on gonadal function. Emerging topics of importance in fertility preservation include pathophysiological, clinical, surgical, epidemiological and psychosocial issues. These topics need to consider different challenges facing the different specialists working in this multidisciplinary field.
This one-day workshop is therefore suitable for oncologists, reproductive medicine specialists and embryologists.

Learning objectives
After attending this live educational conference, participants will be able to:
• Know the key issues regarding fertility and its preservation in cancer patients
• Understand how certain cancer treatments may damage gonadal function
• Be able to utilise appropriate fertility preservation strategies prior to cancer treatment
• Understand current knowledge regarding tissue transplantation and cryopreservation
• Be able to undertake cancer treatment that follows best practices for fertility preservation
• Understand the needs of people with a history of cancer who require fertility treatment

Target audience
This live educational conference is designed for clinicians working in assisted reproductive medicine, and oncologists working with patients of reproductive age, who want to acquire up-to-date information for improving their current clinical practice.

Accreditation
EXCEMED (www.excemed.org) is accredited by the European Accreditation Council for Continuing Medical Education (EACCME®) to provide the following CME activity for medical specialists. The EACCME® is an institution of the European Union of Medical Specialists (UEMS), www.uems.net
The CME “Conference on fertility preservation” held on 4 December 2014 in Paris, France, is designated for a maximum of 6 (six) hours of European CME credits (ECMEC). Each medical specialist should claim only those credits that he/she actually spent in the educational activity. EACCME® credits are recognized by the American Medical Association (AMA) towards the Physician’s Recognition Award (PRA). To convert EACCME® credit to AMA PRA category 1 credit, please contact the AMA.

EXCEMED adheres to the principles of the Good CME Practice Group (gCMEp)
Scientific organisers

Michaël Grynberg  
Service de Médecine de la Reproduction  
Hôpital Jean Verdier  
Bondy, France

René Frydman  
Service de Gynécologie-Obstétrique et Médecine de la Reproduction  
Hôpital Foch  
Suresnes, France

EXCEMED developed this programme in partnership with the French Society of Oncofertility

Share your opinion with us

We are always looking for ways to bring our educational activities to the next level and meet your needs as a healthcare practitioner.

You will be asked to answer a real-time survey during this event, followed by a post-event online survey to find out if the experience met your educational expectations. Your views also help us tailor future initiatives.

Thank you for taking the time to participate.
Faculty members

Claus Yding Andersen
Laboratory of Reproductive Biology
Juliane Marie Centre for Women, Children and Reproduction
University Hospital of Copenhagen
Faculty of Health Science
University of Copenhagen
Copenhagen, Denmark

Kutluk Oktay
Department of Obstetrics & Gynecology,
Medicine, Cell Biology & Anatomy
Division of Reproductive Medicine &
Institute for Fertility Preservation
Westchester Medical Center
Valhalla, NY, USA

Pasquale Patrizio
Yale Fertility Center &
Fertility Preservation program
New Haven, CT, USA

Antonio Pellicer
IVI President
IVI Foundation President
University Medical School
Polytechnic University
Women Health Area
University and Polytechnic Hospital La Fe
Valencia, Spain

Nathalie Rives
Laboratoire de biologie de la reproduction
CECOS, Université de Rouen
Rouen, France

Christophe Sifer
Service de Biologie de la Reproduction
Hôpital Jean Verdier
Bondy, France

Evelyn E. Telfer
Reproductive Biology
The University of Edinburgh
Institute of Cell Biology and
Centre for Integrative Physiology
Edinburgh, UK

Catherine Uzan
Department of Gynaecologic Surgery
Gustave Roussy, Cancer Campus
Grand Paris, Villejuif, France

Christoph C. Zielinski
Comprehensive Cancer Center
General Hospital and Medical University of Vienna
Vienna, Austria
Central European Cooperative Oncology Group (CECOG)
Scientific programme
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**Legend:** IF: Introduction fertility; IO: Introduction oncology; L: Lecture; PD: Panel discussion
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The following faculty provided information regarding significant commercial relationships and/or discussions of investigational or non-EMEA/FDA approved (off-label) uses of drugs:

**Claus Yding Andersen**  Declared no potential conflict of interest.

**Robert Fischer**  Declared no potential conflict of interest.

**René Frydman**  Declared receipt of honoraria or consultation fee from Merck Serono, Ferring, Teve, Organon.

**Michaël Grynberg**  Declared no potential conflict of interest.

**Sibylle Loibl**  Declared no potential conflict of interest.

**Pasquale Patrizio**  Declared to be a member of a company advisory board, board of directors or other similar group of Fertile-Safe Llc.

**Antonio Pellicer**  Declared no potential conflict of interest.

**Nathalie Rives**  Declared no potential conflict of interest.

**Catherine Uzan**  Declared no potential conflict of interest.

**Christoph C. Zielinski**  Declared no potential conflict of interest.

The following faculty have provided no information regarding significant relationship with commercial supporters and/or discussion of investigational or non-EMEA/FDA approved (off-label) uses of drugs as of 27 November 2014.

**Philippe Bouchard**

**Marie-Madeleine Dolmans**

**Jacques Donnez**

**Jean Noël Hugues**

**Dror Meirow**

**Kutluk Oktay**

**Christophe Sifer**

**Evelyn E. Telfer**
Abstracts
L1. Fertility in cancer survivors: critical review of the literature

Sibylle Loibl
German Breast Group, Head Medicine & Research, Neu-Isenburg, Germany

Abstract not in hand at the time of printing.
Chemotherapy and radiation treatment in young female cancer patients can often result in ovarian damage leading to premature ovarian failure (POF) and subsequent infertility. The precise mechanism of damage is multifactorial and varies according to treatment regimens but in many cases a loss of the primordial follicle population has been implicated. The loss of primordial follicles has been shown to occur through several mechanisms, including: follicular apoptosis, blood vessel damage, and follicle activation that may result in the “burn-out” of primordial follicle stockpiles. It is essential to identify the exact mechanisms of chemotherapy-induced ovarian injury in order to develop strategies to avoid this loss of primordial follicles. In addition, growing non-dormant follicles are highly sensitive to chemotherapy leading to acute loss or genetic aberrations in surviving follicles. This information is crucial for planning fertility preservation strategy and for potentially developing novel fertility preserving drugs.
L3. Ethical and moral dilemmas in social egg freezing and banking

Jacques Donnez
Université Catholique de Louvain, Brussels, Belgium

Abstract not in hand at the time of printing.
Fertility preservation (FP) in cancer patients is highly time sensitive and subject to complexities. Many patients are up against a deadline for initiation of chemotherapy, radiotherapy and/or radical surgical procedures even when considering ovarian tissue freezing which does not require ovarian stimulation. Classically for patients undergoing ovarian stimulation for oocyte and embryo freezing, timing of menstruation has to be factored in to this complexity. Recent introduction of random start ovarian stimulation methods has provided more practicality and flexibility, allowing many females to be started on ovarian stimulation regardless of where they are in their menstrual cycle. FP in patients with cancer or other medical conditions is also complicated by the underlying medical complexities such as risk of infection, bleeding, hypercoagulapathy, estrogen-sensitivity and others. For estrogen-sensitive cancers, we have introduced tamoxifen and letrozole co-treatment during ovarian stimulation. Our 14-year-long prospective studies have shown that letrozole protocols result in similar outcomes to standard protocols with fertility preservation rates exceeding 60% and no risk of cancer recurrence after a mean follow-up of around six years. An incidental discovery while performing ovarian stimulation in young women with breast cancer is the relationship between BRCA mutations and diminished ovarian reserve. Starting with our initial report of higher incidence of low response to ovarian stimulation among affected BRCA1-mutation-positive (but not BRCA2) women undergoing ovarian stimulation for fertility preservation, there have been now at least six reports corroborating the diminished ovarian reserve in women with BRCA-mutations. Furthermore, our recent studies showed an important role of DNA repair in oocyte aging and chemotherapy-induced ovarian follicle death. While several other mechanisms have been proposed for chemotherapy-induced damage to ovarian reserve based on rodent studies, we demonstrated that gonadotoxic chemotherapy induces DNA double strand breaks (DSB) in human primordial follicles, triggering apoptotic oocyte death, cell cycle arrest and possibly repair in some instances. Hence, the case of BRCA mutation carriers, where the DNA DSB repair is impaired in oocytes, deserves further study of chemotherapy-induced ovarian damage and fertility preservation outcomes. Future pharmacologic agents which block chemotherapy-induced DNA damage and apoptotic cell death will likely solve many timing issues encountered with current ART technologies.

References:
- Wang, E. T., et al. [2014]. "BRCA1 germline mutations may be associated with reduced ovarian reserve." Fertil Steril. (Epub ahead of print)
Fertility preservation now represents a standard of care for young cancer patients having to undergo gonadotoxic treatment. Ideally, the fertility preservation strategy rests on oocyte or embryo cryopreservation after controlled ovarian hyperstimulation, since they are the most established methods. However, among a large proportion of patients, candidates for fertility preservation are contraindicated for exogenous gonadotropin administration or an urgent gonadotoxic treatment incompatible with ovarian stimulation.

Over the past 20 years, in vitro maturation (IVM) of cumulus-oocyte complexes (COCs) has emerged in the strategy of infertility treatment. It has been initially developed to overcome side effects of exogenous gonadotropin administration such as the ovarian hyperstimulation syndrome. Therefore, patients suffering from polycystic ovarian syndrome had remained the main candidates for such a treatment during the past decades. However, the indications for IVM treatment have remarkably expanded, and now include poor responders to controlled ovarian hyperstimulation, egg donors and patients diagnosed with ovarian resistance syndrome to FSH.

More recently, IVM has been proposed as an option for fertility preservation in women having to undergo gonadotoxic treatments. Indeed, it offers an opportunity to freeze mature oocytes or embryos even in urgent situations. The competence of COCs to mature in vitro is similar whatever the phase of the cycle at which egg retrieval is performed. In addition, IVM requires a less invasive procedure when compared to other techniques of fertility preservation usually proposed in emergencies such as with ovarian tissue cryopreservation.

The potential of vitrified in vitro matured oocytes is still not fully established. However, with more than 5,000 babies born worldwide after performing IVM in infertile patients, we can consider this method as a reliable option for preserving the fertility of young women.
Fertility preservation (FP) has become an important topic in the last decade. Today, there are many Ob/Gyn Departments around the world that have included a program of FP, especially for oncologic patients. This is done in close collaboration with oncologists because timing and indication are the first step when considering FP in a patient. The age of the patient, the extent and type of disease, and the treatment modality to be applied, will be relevant in decision making.

Two main techniques have been readily available in women, ovarian tissue cryopreservation, with subsequent transplantation into the ovarian medulla or a peritoneal pocket, and oocyte (embryo) vitrification.

The experience accumulated in Europe by three experienced groups was recently reviewed (1). In each centre, more than 600 ovarian cortex cryopreservations have been performed and the results of 60 transplantations were analyzed. FSH levels drop to nearly normal levels after 4.5 months, and regular menses was observed in most of the patients. A total of 11 women were pregnant and 12 healthy babies were born in these centres. More than 30 have been born worldwide.

The main issue has been safety due to controversy generated by the replacement of tissue captured before cancer treatment and the risk of introducing malignant cells. While this risk has been discarded for Hodgkin disease and breast cancer, patients with leukemia and non-hodgkin lymphoma still carry this risk, which makes the procedure particularly controversial in teenagers (2). We have developed a new panel of molecular markers to show that, at least in breast cancer patients, the procedure is safe. Nonetheless, much research is conducted to create in vitro systems that override the problem.

Oocyte banking is also an option. Our accumulated experience in 324 and 419 cycles has show that we can retrieve a mean of 7.6 mature oocytes per woman in a single stimulation (3). We have also learned from a different population in whom we accumulate oocytes to increase the chances of becoming pregnant in a single insemination procedure, i.e. the so called low responders, that a mean number of 10 eggs is necessary for freezing to achieve ongoing pregnancy rates close to 60%. In this sense, oncologic patients have relatively good chances of becoming pregnant in the future employing frozen and thawed oocytes. In fact, four transfers have been performed, one resulting in a miscarriage and another a term pregnancy. Thus, we expect that the near future will bring many other pregnancies as has been the case in regular ART.

References:
The issue of fertility preservation must be addressed early in the oncological management of a young patient. Conservative treatment can be offered in some well-defined situations; in other cases the data is more uncertain. Specialized multidisciplinary management [oncologist, surgeon, procreation specialist, and psychologist] has to be proposed. The physician must be able to explain that in some cases conservative treatment is not reasonable, and that the best oncological treatment prevails.
Survival from pediatric cancer has progressed considerably since the last decade due to remarkable improvements in diagnosis and treatment. Unfortunately, chemotherapy and radiotherapy have deleterious effects on gonad functions, more specifically on germ cells. In the pre-pubertal testis, the spermatogonial stem cells (SSCs) are the most sensitive and therefore the most impaired. In young adult males and adolescents, sperm freezing has been proposed for several years as a means of fertility preservation. However, in pre-pubertal boys that do not produce sperm yet, testicular tissue freezing is the only potential strategy to preserve their fertility even though this procedure remains experimental and proposed only in exceptional circumstances. According to data obtained in animal models, the freezing of testicular tissue pieces instead of testicular cell suspension freezing is considered as the preferential method capable of maintaining cell-to-cell interactions between Sertoli and germ cells, and therefore preserving the stem cell niche necessary for the survival and subsequent differentiation of the SSCs. The differentiation of SSCs should be obtained after testicular tissue grafting or germ cell transplantation after recovery. Currently, there is no established standard protocol for testicular tissue freezing but also no fertility restoration procedure in humans to allow sperm generation from the frozen SSCs. Some teams have been involved in Europe in the management of testicular tissue freezing for pre-pubertal boys. This procedure is proposed prior to the initiation of highly gonadotoxic treatment, and essentially proposed before haematopoietic stem cell transplantation.
Abstract not in hand at the time of printing.
The first human live birth from the use of cryopreserved/thawed oocytes was reported in 1986 using the method of slow freezing, but for many years the success rate was modest due to difficulty in minimizing the intracellular damage due to ice formation. It was only recently that a new method, called vitrification, which uses highly concentrated solutions of cryoprotectant and ultra-rapid cooling in liquid nitrogen with open carriers, has been shown to provide high oocyte survival and fertilization rates upon rewarming. Data from several large randomized trials and a recent meta-analysis showed that fertilization and pregnancy rates with cryopreserved/rewarmed oocytes are similar to those obtained with fresh oocytes and that the survival rates of vitrified oocytes are better than those obtained after slow-freeze. Currently the end users of this technology are young, single women with cancer or other medical conditions that, prior to initiating potentially gonadotoxic treatments, wish to preserve their eggs. In addition, in the last two decades there have been significant shifts in socio-economic norms that have resulted in an increasing number of women postponing childbearing, delaying marriage, pursuing educational goals and securing economic stability prior to attempting conception. These women are now also using oocyte freezing as a mean to preserve their age-related chances to reproduce at later time.

However, the clinical outcomes of oocyte freezing/thawing/rewarming must be interpreted with caution and the results will be presented taking into account the context and the patients using the procedure. Oocyte cryopreservation has evolved following four fields of applications:

a) Oocytes from infertile patients (the largest clinical experience has been accumulated in Italy since legal restrictions between 2004 and 2009 had banned embryo cryopreservation);

b) Oocytes from patients with cancer or other medical conditions (very few reports on clinical outcomes since only a few cases utilized the cryopreserved oocytes);

c) Oocytes from donor eggs (with the intent of facilitating the availability of egg donors and creating various cryopreserved egg banks);

d) Oocytes from healthy women (so-called elective fertility preservation, used by women who for a variety of sociological reasons, freeze eggs to somehow prevent an “anticipated future infertility”. Even in this setting, the current utilization rate is still low).

In conclusion, cryopreservation by vitrification of metaphase II oocytes has become a mainstay procedure for women wishing to preserve the potential for future fertility and thousands live births have been reported with no apparent increase in the rate of congenital anomalies compared with United States national statistics for natural conceptions. However, there are still too few births from using cryopreserved oocytes from cancer patients and from elective cases of fertility preservation.
Transplantation of frozen/thawed ovarian tissue for fertility restoration and regaining of fertility and menstrual cycles is rapidly gaining ground as a valid method for fertility preservation alongside cryopreservation of embryos and oocytes. More than 30 healthy children have been born worldwide as a result of this procedure after an estimated 150 women have had tissue transplanted. The procedure is most often carried out by excising one ovary or part of an ovary and leaving the remaining ovary in situ in case the treatment does not destroy all follicles. Until recently all babies born resulted from transplantation of frozen/thawed tissue to the remaining postmenopausal ovary.

In Denmark, cryopreservation of ovarian tissue has been organized with one central laboratory as a national centre that freezes all tissue in close collaboration with three fertility clinics round the country. Totally more than 750 girls and women have had ovarian tissue cryopreserved in Denmark. The youngest girl was 0.5 years old and the oldest 38 years. We have currently cryopreserved ovarian tissue from around 150 girls younger than 16 years of age. The transport model includes that ovarian tissue is excised at the local hospital and transported on ice to the freezing facility, where cryopreservation and storage is performed. In case of transplantation the frozen tissue will transported to the local hospital for the operation back to the patient. This transport model has been validated and has now been used for more than 350 cases.

In Denmark, 43 women have experienced transplantation of frozen/thawed ovarian tissue a total of 55 times (12 women having tissue transplanted twice). All women regained ovarian function and none have experienced relapse as a consequence of the transplantation. Over a period of 20 – 25 weeks levels of FSH gradually return to pre-menopausal levels and menstrual cycles are regained. The longevity of the tissue depends on the age of the woman at tissue retrieval and the amount of tissue transplanted. However, the period of ovarian activity after transplantation is surprisingly long and most women experience return of ovarian function for some years with just a fraction of tissue from one ovary being replaced. A number of women have been pregnant and a total of 8 children have currently been born. The presentation will review our experiences and results with transplantation of cryopreserved ovarian tissue.
The ability to develop human oocytes from the earliest follicular stages through to maturation and fertilisation in vitro could revolutionise fertility preservation practice. This has been achieved in mice where in vitro grown (IVG) oocytes from primordial follicles have resulted in the production of live offspring. However, developing IVG systems to support complete development of human oocytes has been more difficult because of differences in scale of timing and size. The aim of our work is to determine whether complete oocyte development can be achieved from human ovarian tissue grown in a multi-step culture system. We have developed a dynamic three step culture system that supports the activation of primordial follicles (step 1), growth of multilaminar follicles (step 2) and oocyte growth without the need to culture the whole follicle (step 3). Using this system a population of oocytes capable of reaching Metaphase II can be obtained. This presentation will focus on the challenge that lies ahead to improve the quantity and quality of in vitro grown human oocytes and will discuss the testing and safety checks that will be required before this technology could ever be applied in a clinical setting.
Abstract not in hand at the time of printing.
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