The Oncofertility Field Expansion throughout Brazil and Latin America

Dr. Jhenifer Kliemchen Rodrigues, BSc, MSc, PhD
Cancer and life after cancer

Before
Concern about disease

Nowadays
Concern about quality of life
Fertility preservation

Life maintenance
Quality of life
Procreation
Increase in the number of young people who have cancer diagnosis

576,580 new cases of cancer in Brazil in 2016.
Women: 274,230 new cases
Men: 302,350 new cases

Early diagnosis and treatment progress

Increased survival after treatment

Chemotherapy and/or radiotherapy

toxic effect on the gonads

infertility or ovarian failure

Desire maternity/paternity

Jeruss & Woodruff, 2009; Smitz et al., 2010
What is Oncofertility?

Interdisciplinary area that involves Oncology and Reproductive Medicine, which aims to expand the options for fertility preservation for cancer patients.

Oncofertility = Oncology + Fertility

Fertility
Capacity to produce offspring

Oncology
Study of cancer

ONCOFERTILITY
Balancing life-preserving treatments with fertility-preserving options
Low resource setting

GAPS
- Information
- Education
- Options available
- Research
- Cultural issues
Brasil
México
Porto Rico
Peru
Uruguai
Chile
Argentina
Panama
Colombia
Brasil
Oncofertility Consortium
LATIN AMERICA ONCOFERTILITY NETWORK
Organized system of cooperation and action

Group roles

Partnerships

Ideas, tools, actions...

Individual roles
- Mistake: Offer fertility preservation and think that has an Oncofertility Program

- Oncofertility Program IS DIFERENT than only offer fertility preservation options

- Service flowchart
- Psychologist
- Patient navigator (Nursing)
- Know how about techniques
- Partnerships with oncologists
Women
Incidence of amenorrhea after various regimens and medications:
35 - 97% over 40 years
6 - 65% under 40 years

Cyclophosphamide

Old and effective alkylating agent
Each cycle increases the ovarian age in 1.5 to 3 years (depends on dose and frequency)

Treatment for 12 to 16 weeks - increases in more than 10 years the ovarian reproductive age
Embryo cryopreservation

Advantages
- Technique already established;

Disadvantages
- You need to have partner;
- Requires hormonal stimulation;
- Time: It takes on average 15 days to be carried out;
- It can be performed in children and young people.
- Ethical / religious involved, related to the freezing of the excessive number of embryos.
Oocyte cryopreservation

- Survival rate: 92.52%
- Ongoing pregnancy rate: 43.7%

- Approximately 20 oocytes are necessary to achieve a pregnancy.

- Live birth rate/vitrified oocyte: 5-7% Egg donation programs

Results can not be extrapolated for cancer patients.

Donnez e Dolmans, 2015
Oocyte cryopreservation

Advantages
- No need for partner;
- Technique already established (similar to fresh results);
- It can be performed in younger;
- No involvement of ethical / religious issues, it does not involve the freezing of embryos, gametes only.

Disadvantages
- Requires hormonal stimulation;
- Time: It takes on average 15 days to be carried out;
- It can be performed in children.
Oocyte cryopreservation

Brazil: 26-30 centers performs the method
Peru: 1
Chile: 1
Argentina: 1
Panama: 1
Porto Rico: 1
Mexico: 1
Uruguay: 1

live births reported – cancer patients
Live birth after 6 years of oocyte vitrification in a survivor with breast cancer

Eduardo Leme Alves da Motta · Monique Bonavita · José Roberto Alegretti · Maurício Chehin · Paulo Serafini

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Ovarian tissue cryopreservation

**Advantages**
- You do not need to have partner / sperm collection;
- No need for prior hormonal stimulation;
- Time: It takes on average two days to be performed;
- It can be performed in children (prepubertal) or young;
- Preservation of more oocytes;
- No involvement of ethical / religious issues;
- Function can reverse hormone
  - in vitro follicle maturation possibility.

Poiriot et al., 2002; Dolmans et al., 2013

**Disadvantages**
- Technical not established still considered experimental;
- oncologic pathology recurrence risk;
- tissue ischemia risk after reimplantation;
- It is a surgical procedure to tissue removal and the other for reimplantation.

Varghese et al., 2008; Dolmans et al., 2013
The slow freezing has been effective in the preservation of ovarian tissue.

Sánchez et al., 2007

The glazing has been used successfully in ovarian tissue with minimal changes in tissue morphology.

Tao & Del Valle, 2008

? NO consensus!

Kim, 2010
Ovarian tissue cryopreservation

Situação atual

86 live births and 9 ongoing pregnancies!

(84 slow freezing and 2 vitrification)

(Demeestere et al., 2010; Donnez et al., 2011a; Donnez et al., 2011b; Revel et al., 2011; Silber 2012; Dolmans et al., 2013, Sttop et al., 2014; Donnez e Dolmans, 2015; jensen et al., 2016)
FERTILITY PRESERVATION

86 successful births and 9 ongoing pregnancies worldwide in women transplanted with frozen-thawed ovarian tissue: focus on birth and perinatal outcome in 40 of these children

Annette Klüver Jensen¹ · Kirsten Tryde Macklon² · Jens Fedder³ · Erik Ernst⁴ · Peter Humaidan⁵ · Claus Yding Andersen¹

Received: 8 September 2016 / Accepted: 14 November 2016
Ovarian cortex transplantation: time to move on from experimental studies to open clinical application

LIVE BIRTH RATE AFTER OTC AND REIMPLANTATION IN A SERIES OF 111 WOMEN

TABLE 1

<table>
<thead>
<tr>
<th>Team</th>
<th>Transplanted women</th>
<th>Women who conceived (%)</th>
<th>Women who gave birth</th>
<th>Live births (ongoing pregnancies)</th>
<th>Miscarriages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donnez and Dolmans' team</td>
<td>19</td>
<td>7</td>
<td>5</td>
<td>8 (+1)</td>
<td>1</td>
</tr>
<tr>
<td>Andersen’s team</td>
<td>25</td>
<td>8</td>
<td>6</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Pellicer’s team</td>
<td>33</td>
<td>8</td>
<td>4</td>
<td>6 (±3)</td>
<td>3</td>
</tr>
<tr>
<td>Dittrich’s team</td>
<td>20</td>
<td>7</td>
<td>6</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Rozen’s team</td>
<td>14</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>111</td>
<td>32 (29)</td>
<td>23</td>
<td>33 (+4)</td>
<td>7</td>
</tr>
</tbody>
</table>

Note: Data from references 2, 3, 4, and 7. Values are number, except where noted.
* One woman delivered twice.
* One woman delivered three times.
+ One twin delivery.

Ovarian tissue cryopreservation

Brazil: 5 centers that perform the method
Peru: 1
Chile: 1
Argentina: 0
Panama: 0
Porto Rico: 0
Mexico: 0
Uruguay: 0

1 transplantation (Good FSH for 3 months)  
No live births reported yet

Training and knowledge – Europe (Eg: Claus Andersen) and USA (Eg. Mary Zelinksi)
Cryopreservation technique
Transplantation technique
Frozen and Fresh Ovarian Tissue Require Different Culture Media to Promote in Vitro Development of Bovine Preantral Follicles

To cite this article:

Published in Volume: 12 Issue 5: October 23, 2014

Comparison between Slow Freezing and Vitrification in Terms of Ovarian Tissue Viability in a Bovine Model

Comparação da viabilidade do tecido ovariano após congelamento lento e vitrificação em modelo bovino

Ana Luisa Menezes Campos1, Janaina de Souza Guedes1, Jhenifer Klienchem Rodrigues2, Walter Antônio Prata Pace1, Renato Rinco Fontoura3, João Pedro Junqueira Caetano4, Ricardo Mello Marinho1
Combination of techniques

Ovarian tissue cryopreservation
  +
  Puncture of small follicles (~ 5 mm), followed by in vitro oocyte maturation
  +
  Ex vivo oocyte collection and in vitro oocyte maturation
  +
  In vitro follicular maturation

Donnez and Dolmans, 2015
Semen quality of 4480 young cancer and systemic disease patients: baseline data and clinical considerations

Jacques Auger\textsuperscript{1,2}, Nathalie Sermondade\textsuperscript{3} and Florence Eustache\textsuperscript{3,2}
Abstract

Background: Except for testicular cancer and Hodgkin's disease, baseline data on semen quality in case of cancers as well as systemic pathologies of the young adult are scarce or based on low sample size.

Methods: Semen quality in patients having testicular cancer (TGCT, n = 2315), Hodgkin’s disease (HD, n = 1175), non-Hodgkin’s lymphoma (NHL, n = 439), leukemia (L, n = 360), sarcoma (S, n = 208), brain tumour (BT, n = 40), Behcet’s disease (Behcet’s, n = 68) or multiple sclerosis (MS, n = 73) was studied and compared to that of 1448 fertile men candidates for sperm donation (CSD) and 208 partners of pregnant women (PPW). All samples were studied following the same methodology in a single laboratory. Post freezing and thawing semen characteristics were also studied.

Results: The percentage of normozoospermic men was only 37 % for L patients and lower than 60 % for TGCT, NHL, S and BT. The level of sperm production was differently decreased according to pathologies, the median total sperm count in TC and L patients being four times lower (p < 0.01 when compared to CSD and PPW). The lowest percentage of progressively motile spermatozoa was found for L and BT patients (both, p < 0.01 compared to CSD and PPW). The percentage of morphologically normal spermatozoa was also reduced in cancer patients, especially in BT patients. Progressive motility after thawing in patients was about half that observed among candidates for sperm donation. In almost half of the semen of patients with testicular cancer or leukemia, the total number of motile spermatozoa per straw was less than 0.5 × 10^6 compared to 4.3 × 10^6 in CSD.

Conclusions: The present data confirm on large series the deleterious impact of various cancers of the young adult on semen quality, establishing thus baseline data for future studies. Owing to the post-thaw quality of the frozen straws, future fertility projects for the majority of the patients studied (in case there is no post-treatment recovery of spermatogenesis) should necessitate an ICSI to provide the best chance of paternity whatever the fertility check-up in the female partner.

Keywords: Cancer, Systemic disease, Semen quality, Sperm cryopreservation, Sperm banking, Assisted reproductive technologies
Cryopreservation of individually selected sperm: methodology and case report of a clinical pregnancy

Nina Desai · Jeffrey Goldberg · Cynthia Austin ·
Edmund Sabanegh · Tommaso Falcone

Review Article

Human Sperm Cryopreservation: Update on Techniques, Effect on DNA Integrity, and Implications for ART

Marlea Di Santo, Nicoletta Tarozzi, Marco Nadalini, and Andrea Borini

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Academic Editor: James A. Brown
Brazil: 26 - 30 (ART Clinics) + 1 Cancer clinic + 1 ONG
Peru: 1
Chile: 1
Argentina: 1
Panama: 1
Porto Rico: 1
Mexico: 1
Uruguay: 1

2013 – The start
6 centers
Oncologists

Specialist Reproductive Medicine
Goals

- Partnership with Cancer treatment centers: solid connection to oncologists;

- Partnership with Cancer National Societies;

- Partnership with big (National) and small (Regional) cancer patient care non-profit association (Eg: GRAACC – Childhood cancer; Capec, etc)

- To built a standardized guideline for oncofertility program implementation and use of the cryopreservation methods;

- Post-doc: Federal University of Minas Gerais – Clinical Hospital (Public service) To implement an oncofertility program (connection between fertility specialist, oncologist and psychologist in the hospital).

- Specific tools for Latin America countries (Website and books – 1st steps)
Preservação da Fertilidade: Uma Nova Fronteira em Medicina Reproductiva e Oncologia

Editores
Ricardo Mello Marinho
Ana Carolina Japur de Sá Rosa e Silva
João Pedro Junqueira Caetano
Jhenifer Kliemchen Rodrigues

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PARTNERSHIP
Project with colleagues/ Anvisa

CFM
(Brazilian Federal Council of Medicine)
Direct actions of androgens on the survival, growth and secretion of steroids and anti-Müllerian hormone by individual macaque follicles during three-dimensional culture

J.K. Rodrigues1,2,3, P.A. Navarro1, M.B. Zelinski4, R.L. Scouler2,4, and J. Xiu1,3

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Received on September 11, 2014; accepted on December 21, 2014.

Abstract: Androgens play a role in the regulation of follicle formation and the survival of granulosa cells in the ovary. We performed three-dimensional follicle cultures from individual macaque follicles and measured the production of anti-Müllerian hormone (AMH) and androgens. After 7 days of culture, the production of AMH was 3.5 times higher in the androgen-treated cultures compared to the control cultures. These results suggest that androgens have a direct effect on the survival and function of follicles during the early stages of follicle development.

Visão geral sobre preservação da fertilidade feminina depois do câncer

Bruno Ramalho de Carvalho1,2, Jennifer Klimchen Rodriguez3, Jácima Ribeiro Campos1,4, Ricardo Mello Marinho2,3, João Pedro Junqueira Caetano1,4, e Ana Carolina Japar de Sá Rosa e Silva1,4

Estudos demonstram que a gravidez, especialmente a gravidez após um câncer, pode ter benefícios para a qualidade de vida e a saúde mental e física. Portanto, é importante que as mulheres que sobreviveram a um câncer estejam informadas sobre as opções de preservação da fertilidade.

Artigo de revisão

Creating a Global Community of Practice for Oncofertility

Fertility preservation in the cancer setting, known as oncofertility, is a field that requires close collaboration between physicians, basic scientists, clinical researchers, ethicists, lawyers, educators, and social scientists. National Institutes of Health (NIH), NICHD, NICHD-000 was formed to be a scientifically logical resource, both intellectual and monetary, for building this field of practice capable of meeting the needs of patients with cancer. The NIH has expanded its efforts to include new models for fertility preservation, both in vitro and in vivo. The NIH has launched several initiatives to support oncofertility research and clinical trials. These efforts have led to the development of new clinical services and the establishment of a global network of fertility preservation centers. The NIH has also established a registry of patients who are enrolled in fertility preservation studies. This effort has allowed researchers to collect data on fertility outcomes and to identify ways to improve the success of fertility preservation. In addition, the NIH has established a network of centers that provide fertility preservation services to patients with cancer. This network includes centers in the United States, Canada, and Europe.

ABSTRACT

Androgens and endocrine diseases are the main causes of death in Brazil. Estimates for 2013 predict that the occurrence of 150,000 new cases of cancer in Brazilian women aged 15-49 years old each year. In addition, each year, 20,000 women in Brazil are treated for cancer at a young age and are more likely to survive. The clinical use of androgenic agents and anti-Müllerian hormone (AMH) is becoming more common in the clinical setting. The use of AMH and androgens has been shown to increase the likelihood of pregnancy. The study of AMH and androgens in cancer survivors is important for the development of strategies for the reduction of therapeutic sequelae in cancer survivors, ultimately improving the maintenance of their quality of life and the possibility of biological maternity. In conclusion, the article aims to present an overview of possible options for female fertility preservation after a cancer diagnosis at a young age.
Resultados oferecem avanços importantes às tecnologias de reprodução humana, como preservar a fertilidade feminina em casos de câncer.

Avanço em tecnologia de reprodução assistida torna mais próxima a realidade de pacientes com câncer que querem engravidar após a doença. A resposta positiva veio de pesquisas da cientista brasileira Jhenifer Klimchen Rodrigues realizadas nos laboratórios do Oregon National Primate Research Center dos Estados Unidos, com cultivo in vitro da células ovarianas ainda em estágio inicial de desenvolvimento.

O especialista continua: "Estamos muito animados com as possibilidades que essa técnica pode oferecer para as mulheres que sofrem de câncer."

Especialistas avançam em técnica de preservação da fertilidade de pacientes com câncer

Clínica mineira de reprodução assistida e centros internacionais de pesquisa avançam em técnica de maturação de ovulos em laboratorio para uso em pacientes com cancer

Carolina Cotta - Estado de Minas
Publicação: 21/09/2014 09:58

O adiantamento da madurez, o diagnóstico precoce e os avanços no tratamento de alguns tipos de câncer contribuíram para que um número cada vez maior de pacientes em fase reprodutiva sofjam diagnosticados com a doença. É nesse contexto que a relativamente nova oncofertilidade, que envolve a medicina reprodutiva e a oncologia, tem avançado em técnicas que permitem a esses pacientes serem pais ou mães no futuro, ja que o tratamento - com quimio, radioterapia e/ou quimioradiação - pode levar a quadros de subfertilidade ou infertilidade, transitórios ou permanentes.

Uma das esperanças vem de minas. A Rede Pró-Ciliar Medicina Reprodutiva - em parceria com a...
Novas possibilidades de gravidez pós-câncer

Estudo de cientista mineiro propõe cultivo de folículos ovarianos em laboratório, adicionando a eles hormônios masculinos, que mostraram ter papel importante na maturação folicular. Técnica pode ser alternativa para mulheres que querem engravidar depois de terem tido câncer.

Bióloga conduz pesquisa que busca preservar a fertilidade em pacientes com câncer

Online Surveys – Brazil and Latin America

Put data together about:
- number of cancer patients that ask for information and/or go under the procedure for fertility preservation;
- number of centers that has an Oncofertility program well implemented;
- Type of protocols used;
- Etc
Individual roles

Group roles

Partnerships

Organized system of cooperation and action

Ideas, tools, actions...
Gratefulness

Dr. Teresa K. Woodruff, PhD
When oncolgists, scientists and fertility doctors, patients and their families work together, the needs of these patients can be more easily met, turning a devastating diagnosis and interventions optimism towards life.

Teresa Woodruff
Thanks !