Clarisa Gracia MD, MSCE
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Director, Fertility Preservation Program
Penn Fertility Care
University of Pennsylvania
DISCLOSURES

• NONE
OBJECTIVES

• DISCUSS INDICATIONS FOR FERTILITY PRESERVATION

• DISCUSS OPTIONS FOR FERTILITY PRESERVATION INCLUDING EGG FREEZING AND OVARIAN TISSUE CRYOPRESERVATION

• DISCUSS OVARIAN TISSUE CRYOPRESERVATION AND TRANSPLANTATION SUCCESS AND TECHNIQUES
POTENTIAL INDICATIONS FOR FERTILITY PRESERVATION

• FERTILITY THREATENING TREATMENTS
  • GONADOTOXIC THERAPIES FOR MEDICAL DISEASES
  • OOPHORECTOMY FOR DISEASE OR PROPHYLACTIC (BRCA)
  • TRANSGENDER PATIENTS UNDERGOING OVARIAN SUPPRESSION OR GONADECTOMY

• CONDITIONS ASSOCIATED WITH POF
  • TURNER SYNDROME, GONADAL DYSGENESIS
  • FRAGILE X PREMUTATION, OTHER X CHROMOSOME ABNORMALITIES
  • GALACTOSSEMA, AUTOIMMUNE POLYENDOCRINOPATHY

• TO CIRCUMVENT AGE RELATED DECLINE IN FERTILITY
Impact of Cancer Therapies: Females

Cancer Therapies destroy ovarian follicles and Accelerate Ovarian Aging

Type and timing of exposure influences puberty and menstrual function

Number of follicles in the ovaries

Pubertal Failure

Premature Menopause <40 years

Early Menopause

20 weeks in utero 6,000,000

Birth 1,000,000

Puberty 300,000

Menopause “0”
FERTILITY PRESERVATION IN FEMALES
ASSISTED REPRODUCTIVE TECHNIQUES

- Freeze Embryos
- Freeze Mature Oocytes
- Freeze Ovarian Tissue

Established Methods

Mature Oocyte
Sperm
“In patients facing infertility due to chemotherapy, oocyte cryopreservation is recommended with appropriate counseling”
### USA: 2016 NATIONAL SART DATA

<table>
<thead>
<tr>
<th></th>
<th>Frozen Donor Eggs</th>
<th>Fresh Donor Eggs</th>
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</thead>
<tbody>
<tr>
<td>Number of recipient cycle starts</td>
<td>3373</td>
<td>4649</td>
</tr>
<tr>
<td>Number transfers</td>
<td>2760</td>
<td>4190</td>
</tr>
<tr>
<td>Mean number of embryos transferred</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Live birth/transfer*</td>
<td>44%</td>
<td>55%</td>
</tr>
<tr>
<td>Live birth/ cycle</td>
<td>36.2%</td>
<td>50%</td>
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</table>

*calculated from SART data
OOCYTE CRYOPRESERVATION

• GOOD OPTION BEFORE CANCER THERAPY AND CAN BE COMPLETED SAFELY AND QUICKLY (2-3 WEEKS)

• ADVANTAGES
  • PROVEN TECHNOLOGY IN SOME POPULATIONS
  • PGD IS AN OPTION
  • MAY BE USED IN A GESTATION CARRIER

• DISADVANTAGES
  • LIMITED NUMBER OF EGGS EACH TIME
  • COMPLEX PROCESS, TAKES TIME
  • EXPENSIVE
  • MAY NOT BE SUCCESSFUL OR SAFE IMMEDIATELY AFTER CHEMOTHERAPY EXPOSURE
  • NOT POSSIBLE BEFORE PUBERTY
OVARIAN TISSUE BANKING

• ADVANTAGES
  • CAN CRYOPRESERVE THOUSANDS OF EGGS AT ONE TIME
  • SIMPLE PROCEDURE
  • LITTLE DELAY IN STARTING THERAPY
  • MAY PERFORM AFTER EXPOSURE TO SOME CHEMOTHERAPY
  • ONLY OPTION FOR PREPUBERTAL GIRLS

• DISADVANTAGES
  • REQUIRES SURGERY TO REMOVE AND REPLACE TISSUE LATER
  • RISK OF TRANSPLANTATION IS A CONCERN
  • PGD AND GESTATIONAL CARRIER UNLIKELY OPTIONS
    • IVF AFTER TRANSPLANT IS INEFFECTIVE
    • IN VITRO MATURATION TECHNIQUES NOT CLINICALLY AVAILABLE
Ovarian tissue cryopreservation: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

- OVARIAN TISSUE CRYOPRESERVATION AND SUBSEQUENT TRANSPLANT MAY BE OFFERED TO CAREFULLY SELECTED PATIENTS AS AN EXPERIMENTAL PROTOCOL.
  - PREPUBERTAL GIRLS
  - WOMEN WITH HORMONE-SENSITIVE MALIGNANCIES
  - ANTICIPATING HEMATOPOIETIC STEM CELL TRANSPLANTATION (ANY INDICATION)
  - FEMALES WITH GENETIC MUTATIONS THAT POSE A HIGH RISK FOR PREMATURE OVARIAN FAILURE
  - PRINCIPALLY FOR THOSE WHO CANNOT PURSUE NON-EXPERIMENTAL TECHNIQUES
CASE OF MARY
THANKSGIVING 2009

• 35 YEAR OLD MARRIED NULLIPAROUS FEMALE WHO PRESENTED TO HER PRIMARY PHYSICIAN WITH SHORTNESS OF BREATH, DRY COUGH, NIGHT SWEATS, AND CHEST DISCOMFORT

• CHEST X RAY - 10 CM MEDIASTINAL MASS

• PET/CT DEMONSTRATED PANCREATIC AND LIVER INFILTRATION

• BIOPSY PROVEN MEDIASTINAL LARGE B-CELL LYMPHOMA

• HOSPITALIZED WITH THE INTENT OF IMMEDIATE CHEMOTHERAPY WITH CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRIrine, PREDNSONE AND RITUXIMAB (R-CHOP)
CASE OF MARY

• SHE REFUSED CHEMOTHERAPY INITIALLY BECAUSE SHE WAS VERY CONCERNED ABOUT THE EFFECTS ON HER FUTURE FERTILITY

• SHE WAS INFORMED OF THE MODERATE RISK OF INFERTILITY AND OVARIAN FAILURE RELATED TO THIS CHEMOTHERAPEUTIC REGIMEN

• OPTIONS FOR FERTILITY PRESERVATION WERE DISCUSSED BUT SHE WAS NOT A CANDIDATE FOR OOCYTE OR EMBRYO CRYOPRESERVATION

• SHE WAS OFFERED OVARIAN TISSUE CRYOPRESERVATION UNDER PENNS PROTOCOL AS PART OF THE ONCOFERTILITY CONSORTIUM
OVARIAN TISSUE CRYOPRESERVATION

- AMH = 0.3 NG/ML PRIOR TO CHEMOTHERAPY

- AFTER ONE ROUND OF CHEMOTHERAPY, A LAPAROSCOPIC OVARIAN BIOPSY WAS OBTAINED

- THE TISSUE WAS PROCESSED AND CRYOPRESERVED USING A SLOW FREEZE TECHNIQUE
OVARIAN TRANSPLANT

• 3 YEARS POST TREATMENT, SHE WAS MENOPAUSAL
  • FSH>100, E2 <30, AMH <0.016

• SHE DESIRED OTT
  • IRB WRITTEN/APPROVED
  • ONCOLOGY, MFM, AND PSYCHOLOGICAL CONSULT
  • SEMEN ANALYSIS

• HYSTEROSCOPY, LAPAROSCOPY, TUBAL STUDY, OVARIAN TRANSPLANT
HORMONE CHANGES AFTER TRANSPLANT

- Estradiol
- FSH
- Progesterone

Improved symptoms
Menstrual periods

FSH = 130

Transplant
2 months
3 months
4 months
5 months
6 months

Ovulation
OVARIAN TISSUE TRANSPLANTATION SUCCESS

Summary of Births from Orthotopic transplantation

First Live Birth 2004 (Lancet) Donnez

Donnez, NEJM 2017
SUCCESS OF OVARIAN TISSUE TRANSPLANTATION

OVER 130 LIVE BIRTHS REPORTED SINCE 2004

<table>
<thead>
<tr>
<th>Meta-analysis of 309 transplants in 255 patients</th>
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<tbody>
<tr>
<td>Age at cryopreservation(range)</td>
<td>29.3 (9-44)</td>
</tr>
<tr>
<td>Age at transplant</td>
<td>33 (13-45)</td>
</tr>
<tr>
<td>Endocrine function rate</td>
<td>63.9% (55/86)</td>
</tr>
<tr>
<td>Cumulative ongoing pregnancy/women</td>
<td>38% (65/172)</td>
</tr>
<tr>
<td>At least 1 pregnancy</td>
<td>28% (49/172)</td>
</tr>
<tr>
<td>Unassisted conceptions</td>
<td>62.3%</td>
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Donnez, NEJM 2017,
Pacheco et al. Reproductive Sciences 2017
SUCCESS OF OOCYTE VS. OVARIAN TISSUE CRYOPRESERVATION
SINGLE PRACTICE EXPERIENCE

<table>
<thead>
<tr>
<th></th>
<th>Oocyte N=49</th>
<th>Ovarian tissue N=44</th>
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<tbody>
<tr>
<td>Clinical pregnancies</td>
<td>40.8% (20/49)</td>
<td>34% (15/44)</td>
</tr>
<tr>
<td>Live Births</td>
<td>32.6% (16/49)</td>
<td>23% (10/44)</td>
</tr>
</tbody>
</table>

RR = 1.39 [95% CI 0.95–2.03]

Since 2005, less than 7% of patients came back to use their reproductive tissues

Diaz-Gracia Fert Steril 2018
Transplantation of frozen thawed ovarian tissue demonstrate high reproductive performance and the need to revise restrictive criteria

Dror Meirow, M.D., a,b Hila Ra’anani, M.D., a,b Moran Shapira, M.D., a,b Masha Brenghausen, Ph.D., a,b Chaim Sanaz Derech, B.Sc., a Sarit Aviel-Ronen, M.D., Ph.D., c Ninette Amerligio, M.D., d Eyal Schiff, M.D., b Raoul Orvieto, M.D., a,b and Jehoshua Dor, M.D. a,b

a Fertility Preservation, IVF Unit, b Division of Obstetrics and Gynecology, c Department of Pathology and Talpiot Medical Leadership Program, and d Cancer Research Center, Sheba Medical Center, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel
ORTHOTOPIC TRANSPLANT TECHNIQUES

THANKS TO ALL WHO CONTRIBUTED VIDEOS

RALF DITTRICH
MICHEAL VON WOLFF
DROR MEIROW
SHERMAN SILBER
KUTLUK OKTAY
• 3 COUNTRIES (GERMANY/AUSTRIA/SWITZERLAND) HAVE 101 CENTERS

• FOUNDED IN 2006

• COLLECTED OVER 2500 OVARIAN TISSUE SAMPLES IN CANCER PATIENTS/74 TRANSPLANTS

• > 65% WITH HORMONAL FUNCTION AT 1 YEAR

• 17/74 (23%) LIVE BIRTH RATE PER WOMAN

• 9/40 (23%) LIVE BIRTH RATE WITH 1ST TRANSPLANT AFTER POI

• NONE AFTER PELVIC RADIATION

Van der Ven 2016
OTC SHOULD BE OFFERED TO:

- WOMEN LESS THAN 40 YEARS OF AGE
- IDEALLY BEFORE EXPOSURE TO CHEMOTHERAPY TO MAXIMIZE FOLLICLES BUT MAY BE PERFORMED AFTER SOME CHEMOTHERAPY

LAPAROSCOPY UNLESS LAPAROTOMY PLANNED

- COORDINATE WITH ANOTHER PROCEDURE

AVOID TAKING TISSUE FROM OVARY WITH CYSTS

USE COLD SCISSORS

REMOVE AT LEAST 1/3 – 1 OVARY

SEND SMALL FRAGMENT TO PATHOLOGY
TISSUE TRANSPORT AND DISSECTION

• COURIER FROM OPERATING ROOM TO LABORATORY ON ICE IN HOLDING MEDIA

• TRANSPORT VIA MAIL COURIER MAY BE REASONABLE
  • DANISH AND GERMAN EXPERIENCE DEMONSTRATED PREGNANCIES FROM OTC UP TO 24 HOURS LATER

• DISSECTION WITH SCISSORS OR TISSUE SLICER
  • 1-1.5 MM THICK
  • 5MM – 10MM WIDE

• CONTROVERSY RE: SLOW FREEZE VS. VITRIFICATION

Beckmann 2018
Andersen 2008
TRANSPLANTATION

- CANDIDATES: POI OR DOR FOR ACHIEVING PREGNANCY
- ASSESS FERTILITY: SEMEN ANALYSIS, UTERINE/TUBAL ASSESSMENT
- EVALUATE RISKS OF PREGNANCY AND TRANSPLANTATION
- LAPAROSCOPIC TO PELVIC WALL OR ON OVARY
- MARK WITH CLIPS
- TRANSPLANT 1/3-1/2 OF TISSUE
- POST TRANSPLANT MONITOR OVARIAN FUNCTION
- UNASSISTED PREGNANCY, IUI VS. IVF
  - DEPENDS ON OVARIAN RESERVE AND OTHER FACTORS
PERITONEAL POCKET TECHNIQUE

THANKS TO: Ralf Dittrch, Matthias Beckmann et al. Frauenklinik, University of Erlangen, Germany
THANKS TO: Micheal vonWolff and Micheal Mueller
University Women’s Hospital, Bern Switzerland
SHEBA FERTILITY PRESERVATION CENTER, ISRAEL

- SINGLE CENTER REPORTED 31 TRANSPLANTS
  - PREFERENCES TRANSPLANT TO OVARY USING TUNNEL TECHNIQUE
  - 13/31 (42%) PREGNANCY RATE OVERALL
    - <35 YEARS OF AGE 48% PREGNANCY RATE
    - >35 YEARS OF AGE 17% PREGNANCY RATE
    - 8/14 (61%) WOMEN WITH PRIOR CHEMO EXPOSURE CONCEIVED

Meirow 2018
OVARIAN TUNNEL TECHNIQUE

THANKS TO: DROR MEIROW
THE SHEBA MEDICAL CENTER, ISRAEL
MICROSURGICAL OPEN TECHNIQUE

https://youtu.be/6DKVwZCr_Vo

THANKS TO SHERMAN SILBER INFERTILITY CENTER OF ST LOUIS
ROBOTIC APPROACHES

THANKS TO: KUTLUK OKTAY
YALE MEDICAL CENTER
RISK OF RESEEDING CANCER

• Appears to be highest with leukemia
  • Ovarian tissue from 18 patients with leukemia (CML or ALL) was transplanted in mice and resulted in tumors/evidence of cancer

• Systematic review of 289 studies:
  • Great concern: leukemia, ovarian, BRCA mutation
  • Serious concern: gastric, colorectal, endometrial
  • Less concern: cervical, breast
  • Least concern: lymphoma

METHODS USED TO IMPROVE THE SAFETY OF OVARIAN TISSUE TRANSPLANTATION IN HIGH RISK PATIENTS - LEUKEMIA

Histology, IHC

Sampled thawed ovarian tissue

Xenotransplantation

FISH

Flow Cytometry

NGS

PCR

Dror Meirow Slide
First delivery in a leukemia survivor after transplantation of cryopreserved ovarian tissue, evaluated for leukemia cells contamination

Followed by Additional [spontaneous pregnancy]

2nd delivery- health baby

Shapira et al. 2018
Dror Meirow Slide
PENN’S ONCOFERTILITY PROGRAM

• COMPREHENSIVE CLINICAL AND RESEARCH PROGRAM STARTED IN 2007

• FERTILITY PRESERVATION PROGRAM
  • WE OFFER ESTABLISHED AND EXPERIMENTAL TECHNIQUES
  • WOMEN AND GIRLS: EMBRYO, EGG AND OVARIAN TISSUE BANKING
    • OVER 250 OVARIAN STIMULATION CYCLES IN CANCER PATIENTS
    • 102 OVARIAN TISSUE CRYOPRESERVATION CASES, 1 TRANSPLANT
    • HOSPITAL IVF PROGRAM FOR SICK PATIENTS
  • MEN AND BOYS: SPERM AND TESTICULAR TISSUE BANKING

• SURVIVORSHIP REPRODUCTIVE CARE
  • THIRD PARTY REPRODUCTION
  • HORMONE REPLACEMENT THERAPY, CONTRACEPTION
EXPERIENCE AT PENN WITH OTC

• OFFER OTC UNDER EXPERIMENTAL PROTOCOL AT PENN AND CHOP (ONCOFERTILITY CONSORTIUM)

• 102 OVARIAN TISSUE CRYOPRESERVATION CASES SINCE 2008
  • AGES 1-37 (80% < 21 YEARS OF AGE)
  • 70% PRIOR EXPOSURE TO CHEMOTHERAPY
  • HIGH RISK THERAPY PLANNED (OFTEN BMT, PELVIC XRT)
  • 90% COMBINED WITH ANOTHER SCHEDULED PROCEDURE

• DONOR FUND COVERS PEDIATRIC CASES, INSURANCE HAS COVERED SOME ADOLESCENT/ADULT CASES
LOOKING AHEAD

• GREAT STRIDES HAVE BEEN MADE TO EXPAND THE REPRODUCTIVE OPTIONS OF PATIENTS WITH CANCER AND OTHER FERTILITY THREATENING CONDITIONS

• GLOBAL COLLABORATION IN RESEARCH AND CLINICAL CARE IS ESSENTIAL TO DISSEMINATE NEW STRATEGIES INCLUDING OVARIAN TISSUE TRANSPLANTATION
“AS A YOUNG, SINGLE, WOMAN DIAGNOSED WITH CANCER THE SCARIEST PART OF DIAGNOSIS WAS THE FEAR THAT MY ULTIMATE GOAL IN LIFE WOULD BE TAKEN FROM ME, THE OPPORTUNITY TO BECOME A MOTHER. THE ABILITY TO MEET WITH DOCTORS AND DISCUSS FERTILITY PRESERVATION PRIOR TO TREATMENT OFFERED COMFORT DURING A VERY CHAOTIC TIME WHEN MAJOR HEALTH DECISIONS WERE MADE IN A MATTER OF DAYS. IT WAS REASSURING TO KNOW THAT DESPITE THE RISK OF MEDICAL TREATMENT THAT I STILL HAD FERTILITY OPTIONS WHEN TREATMENT WAS FINISHED.” 25 YEAR OLD BREAST CANCER SURVIVOR
THANK YOU!