

OVARIAN TISSUE TRANSPLANTATION

ONCOFERTILITY CONFERENCE NOV 2018



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DISCLOSURES

- NONE

OBJECTIVES

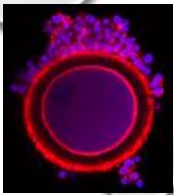
- DISCUSS INDICATIONS FOR FERTILITY PRESERVATION
- DISCUSS OPTIONS FOR FERTILITY PRESERVATION INCLUDING EGG FREEZING AND OVARIAN TISSUE CRYOPRESERVATION
- DISCUSS OVARIAN TISSUE CRYOPRESERVATION AND TRANSPLANTATION SUCCESS AND TECHNIQUES

POTENTIAL INDICATIONS FOR FERTILITY PRESERVATION

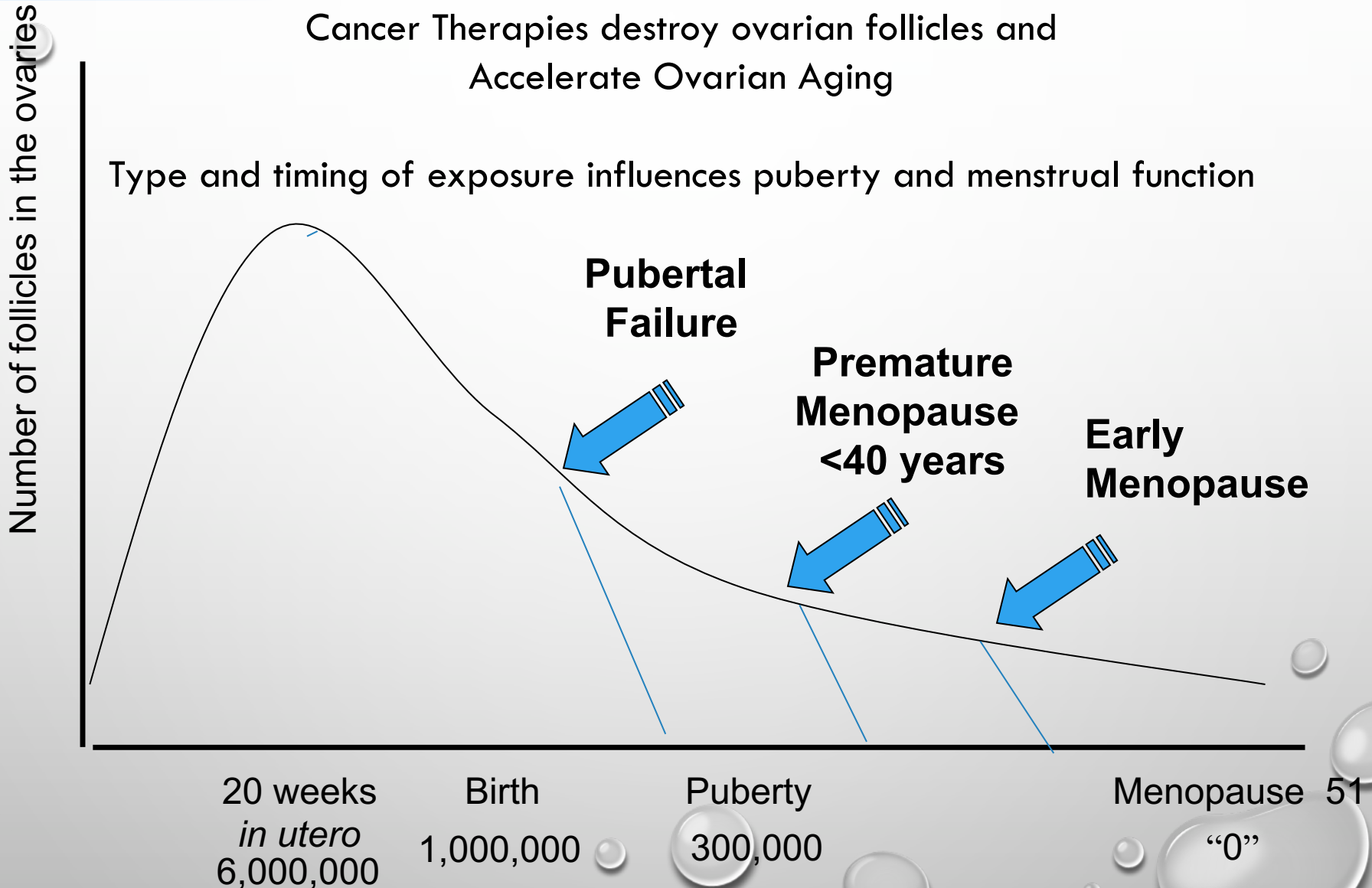
- FERTILITY THREATENING TREATMENTS
 - GONADOTOXIC THERAPIES FOR MEDICAL DISEASES
 - OOPHORECTOMY FOR DISEASE OR PROPHYLACTIC (BRCA)
 - TRANSGENDER PATIENTS UNDERGOING OVARIAN SUPPRESSION OR GONADECTOMY

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

- TO CIRCUMVENT AGE RELATED DECLINE IN FERTILITY

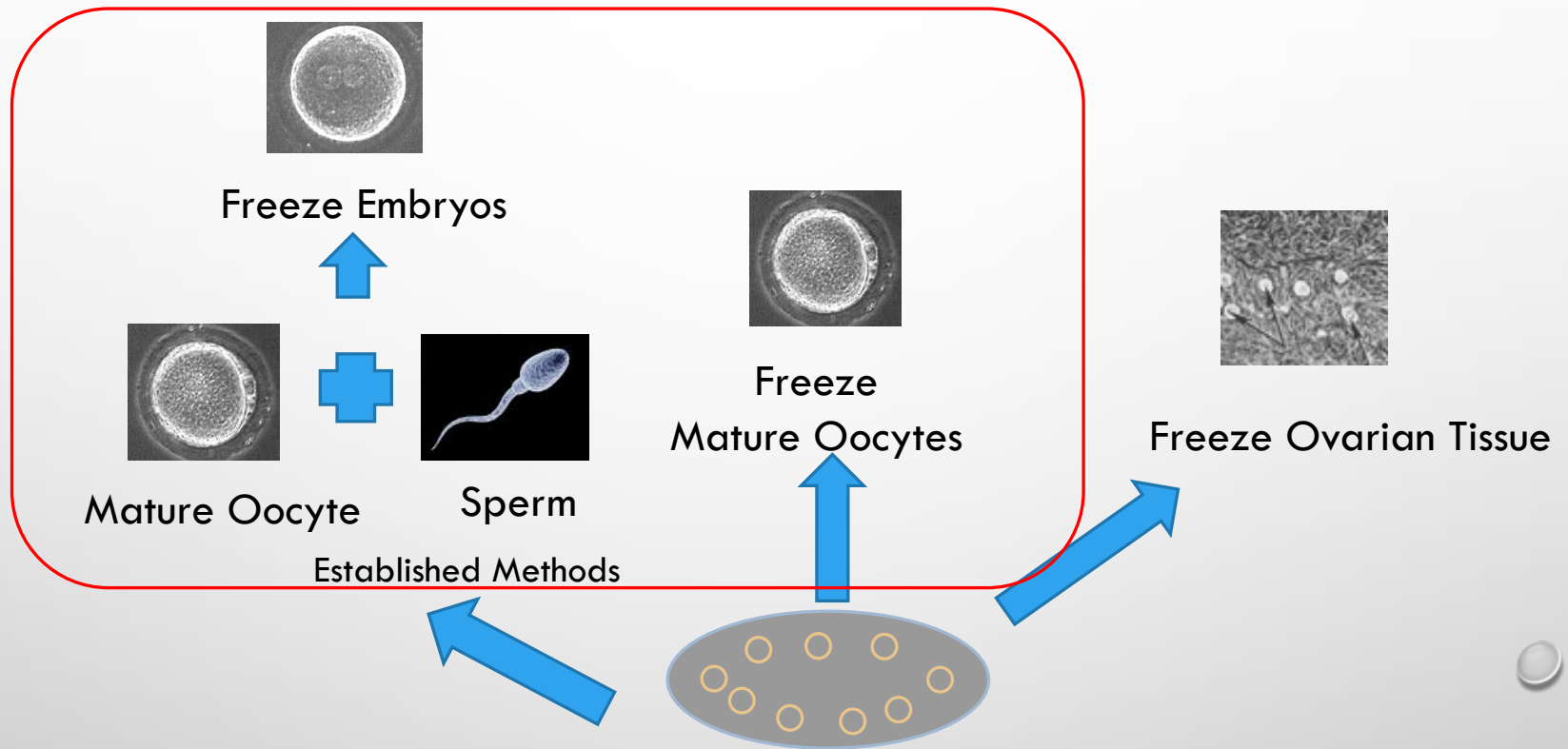


Impact of Cancer Therapies: Females



FERTILITY PRESERVATION IN FEMALES

ASSISTED REPRODUCTIVE TECHNIQUES



Mature oocyte cryopreservation: a guideline

The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

Society for Reproductive Medicine and Society for Assisted Reproductive Technology, Birmingham, Alabama

“In patients facing infertility due to chemotherapy, oocyte cryopreservation is recommended with appropriate counseling”

OOCYTE CRYOPRESERVATION SUCCESS

USA: 2016 NATIONAL SART DATA

	Frozen Donor Eggs	Fresh Donor Eggs
Number of recipient cycle starts	3373	4649
Number transfers	2760	4190
Mean number of embryos transferred	1.5	1.5
Live birth/transfer*	44%	55%
Live birth/ cycle	36.2%	50%

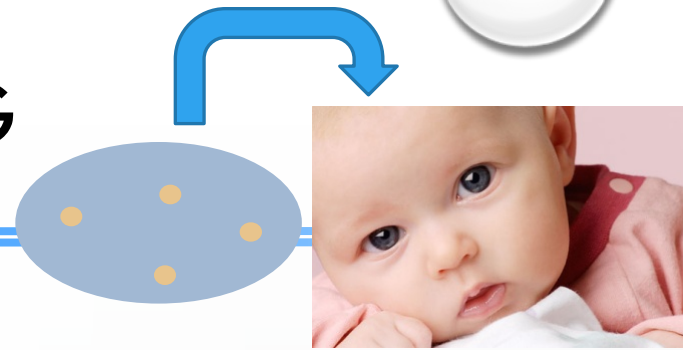
*calculated from SART data

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 INEFFICIENT
 - 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

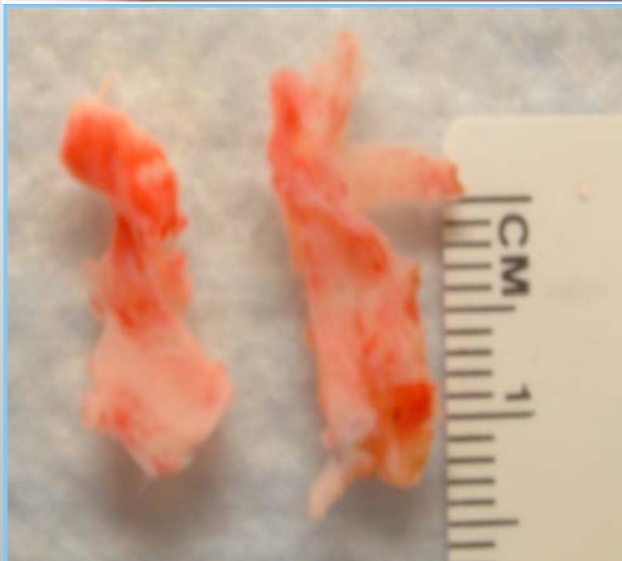
THANKSGIVING 2009

- 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, VINCRISTINE, PREDNISONE AND RITUXIMAB (R-CHOP)

CASE OF MARY

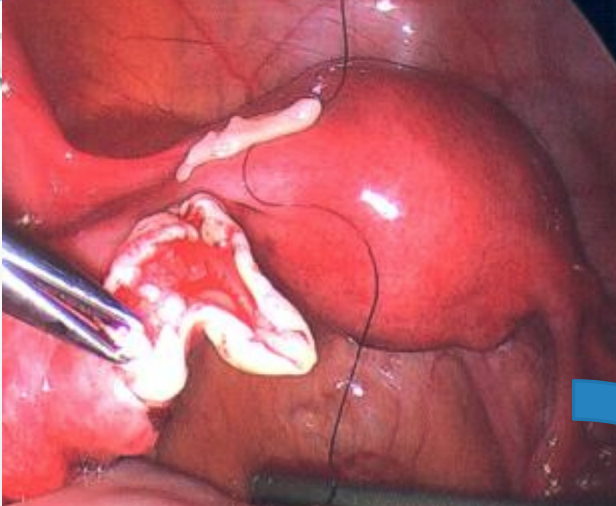
- SHE REFUSED CHEMOTHERAPY INITIALLY BECAUSE SHE WAS VERY CONCERNED ABOUT THE EFFECTS ON HER FUTURE FERTILITY
- SHE WAS INFORMED OF THE MODERATE RISK OF INFERTILITY AND OVARIAN FAILURE RELATED TO THIS CHEMOTHERAPEUTIC REGIMEN
- OPTIONS FOR FERTILITY PRESERVATION WERE DISCUSSED BUT SHE WAS NOT A CANDIDATE FOR OOCYTE OR EMBRYO CRYOPRESERVATION
- SHE WAS OFFERED OVARIAN TISSUE CRYOPRESERVATION UNDER PENNS PROTOCOL AS PART OF THE ONCOFERTILITY CONSORTIUM

OVARIAN TISSUE CRYOPRESERVATION



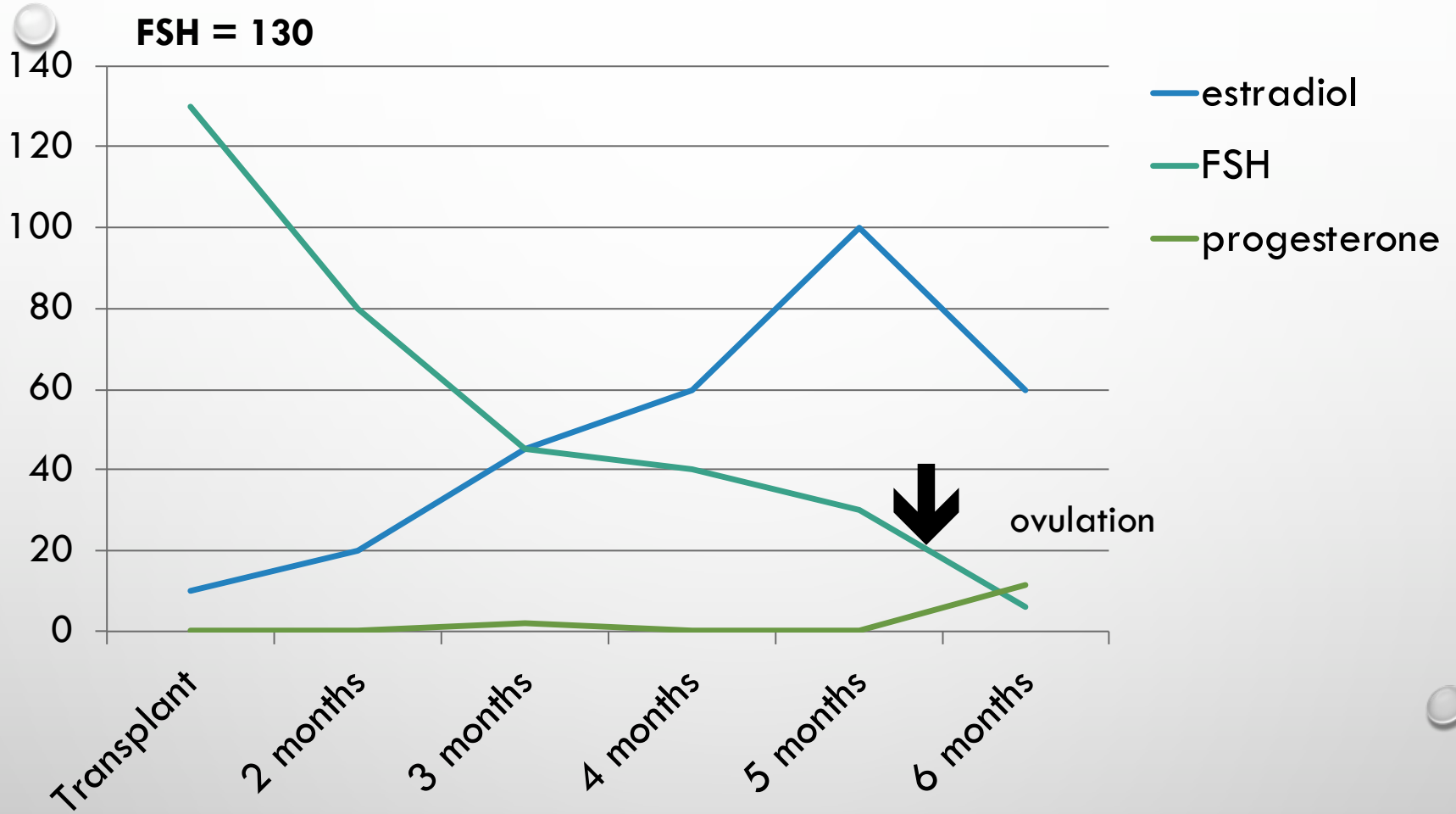
- AMH = 0.3 NG/ML PRIOR TO CHEMOTHERAPY
- AFTER ONE ROUND OF CHEMOTHERAPY, A LAPAROSCOPIC OVARIAN BIOPSY WAS OBTAINED
- THE TISSUE WAS PROCESSED AND CRYOPRESERVED USING A SLOW FREEZE TECHNIQUE

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



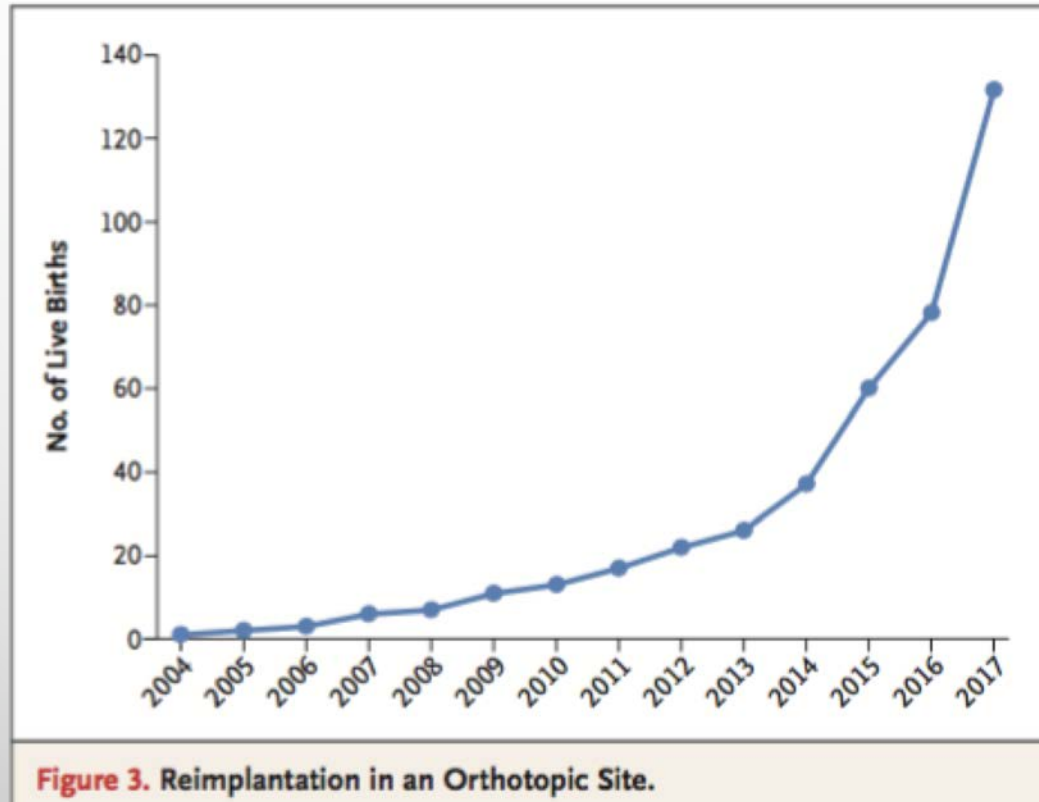
Improved symptoms
Menstrual periods



OVARIAN TISSUE TRANSPLANTATION SUCCESS

Summary of Births from Orthotopic transplantation

First Live Birth 2004 (Lancet) Donnez



SUCCESS OF OVARIAN TISSUE TRANSPLANTATION

OVER 130 LIVE BIRTHS REPORTED SINCE 2004

Meta-analysis of 309 transplants in 255 patients

Age at cryopreservation(range)	29.3 (9-44)
Age at transplant	33 (13-45)
Endocrine function rate	63.9% (55/86)
Cumulative ongoing pregnancy/women	38% (65/172)
At least 1 pregnancy	28% (49/172)
Unassisted conceptions	62.3%

Donnez, NEJM 2017,
Pacheco et al. Reproductive Sciences
2017

SUCCESS OF OOCYTE VS. OVARIAN TISSUE CRYOPRESERVATION

SINGLE PRACTICE EXPERIENCE

	Oocyte N=49	Ovarian tissue N=44
Clinical pregnancies	40.8% (20/49)	34% (15/44)
Live Births	32.6% (16/49)	23% (10/44)

RR = 1.39 [95% CI 0.95–2.03]

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

SHOULD WE MAKE OVARIAN TISSUE CRYOPRESERVATION AND TRANSPLANTATION NON-EXPERIMENTAL?

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 Ameriglio, 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

FertiPROTEKT

Netzwerk für fertilitätsprotektive Maßnahmen

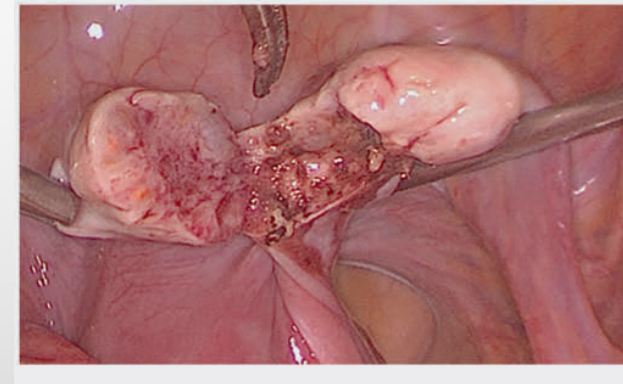


- 3 COUNTRIES (GERMANY/AUSTRIA/SWITZERLAND) HAVE 101 CENTERS
 - FOUNDED IN 2006
 - COLLECTED OVER 2500 OVARIAN TISSUE SAMPLES IN CANCER PATIENTS/74 TRANSPLANTS
 - > 65% WITH HORMONAL FUNCTION AT 1 YEAR
 - 17/74 (23%) LIVE BIRTH RATE PER WOMAN
 - 9/40 (**23%**) LIVE BIRTH RATE WITH 1ST TRANSPLANT AFTER POI
 - NONE AFTER PELVIC RADIATION

FertiPROTEKT

Netzwerk für fertilitätsprotective Maßnahmen

- 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

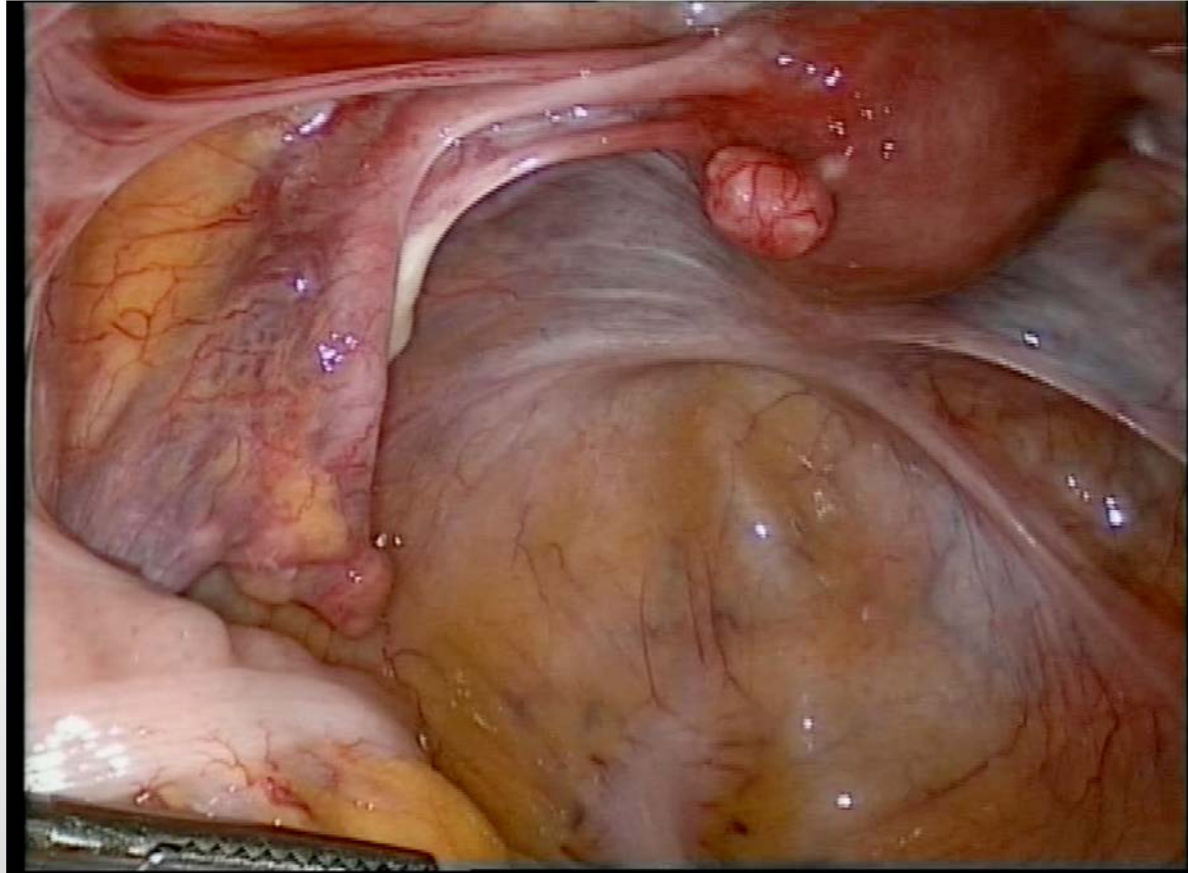
- COURIER FROM OPERATING ROOM TO LABORATORY ON ICE IN HOLDING MEDIA
- TRANSPORT VIA MAIL COURIER MAY BE REASONABLE
 - DANISH AND GERMAN EXPERIENCE DEMONSTRATED PREGNANCIES FROM OTC UP TO 24 HOURS LATER
- DISSECTION WITH SCISSORS OR TISSUE SLICER
 - 1-1.5 MM THICK
 - 5MM – 10MM WIDE
- CONTROVERSY RE: SLOW FREEZE VS. VITRIFICATION



TRANSPLANTATION

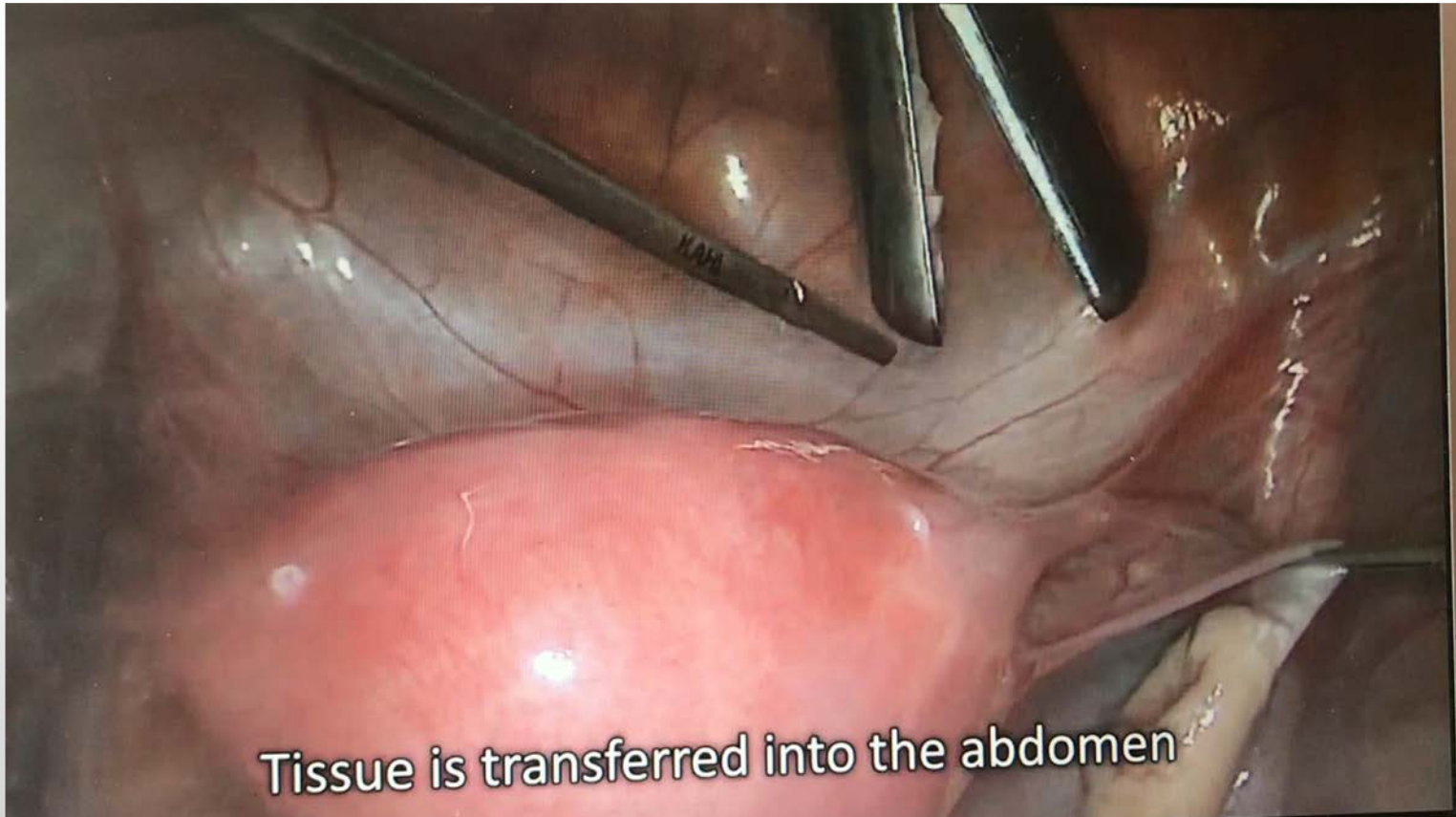
- CANDIDATES: POI OR DOR FOR **ACHIEVING PREGNANCY**
- ASSESS FERTILITY: SEMEN ANALYSIS, UTERINE/TUBAL ASSESSMENT
- EVALUATE RISKS OF PREGNANCY AND TRANSPLANTATION
- LAPAROSCOPIC TO PELVIC WALL OR ON OVARY
- MARK WITH CLIPS
- TRANSPLANT 1/3-1/2 OF TISSUE
- POST TRANSPLANT MONITOR OVARIAN FUNCTION
- UNASSISTED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

PERITONEAL POCKET TECHNIQUE



THANKS TO: Ralf Dittich, Matthias Beckmann et al.
Frauenklinik, University of Erlangen, Germany

OVARIAN TRANSPLANT



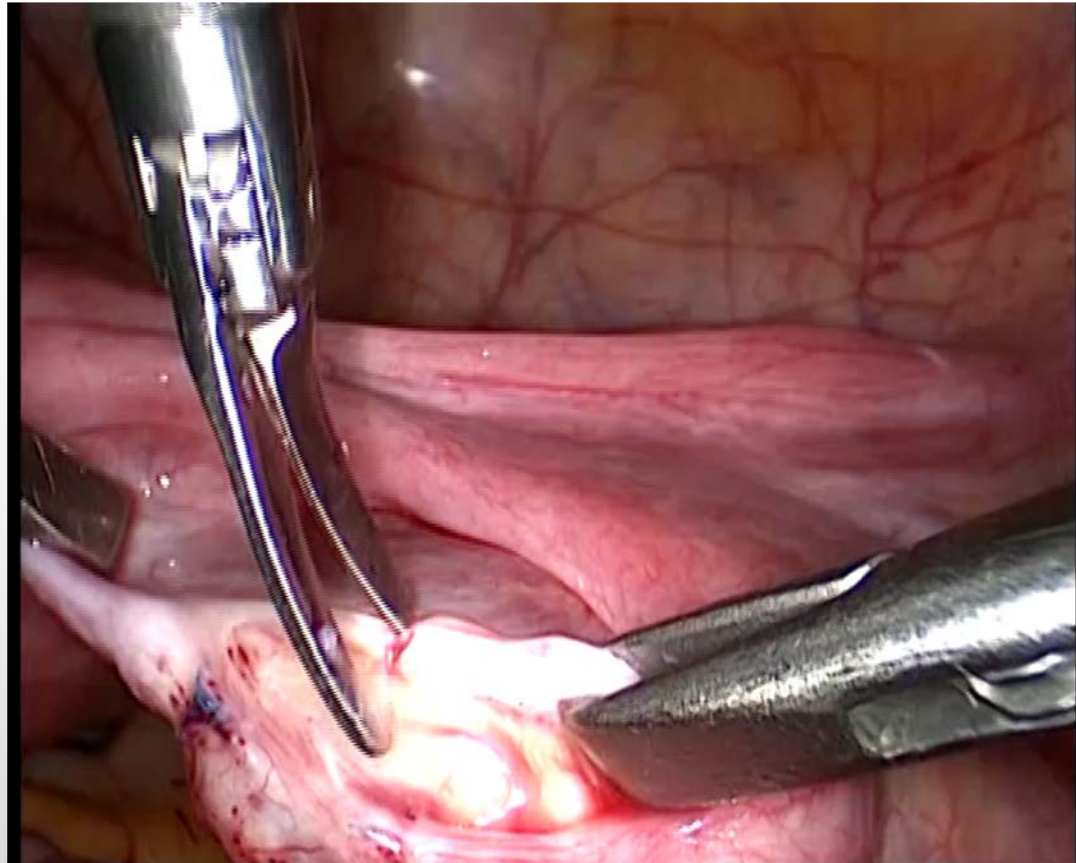
Tissue is transferred into the abdomen

THANKS TO: Micheal vonWolff and Micheal Mueller
University Women's Hospital, Bern Switzerland

SHEBA FERTILITY PRESERVATION CENTER, ISRAEL

- SINGLE CENTER REPORTED 31 TRANSPLANTS
 - PREFERS 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

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

Technique-1

Ovarian autotransplantation to contralateral ovary
using robotic assistance and Alloderm

THANKS TO: KUTLUK OKTAY
YALE MEDICAL CENTER

RISK OF RESEEDING CANCER

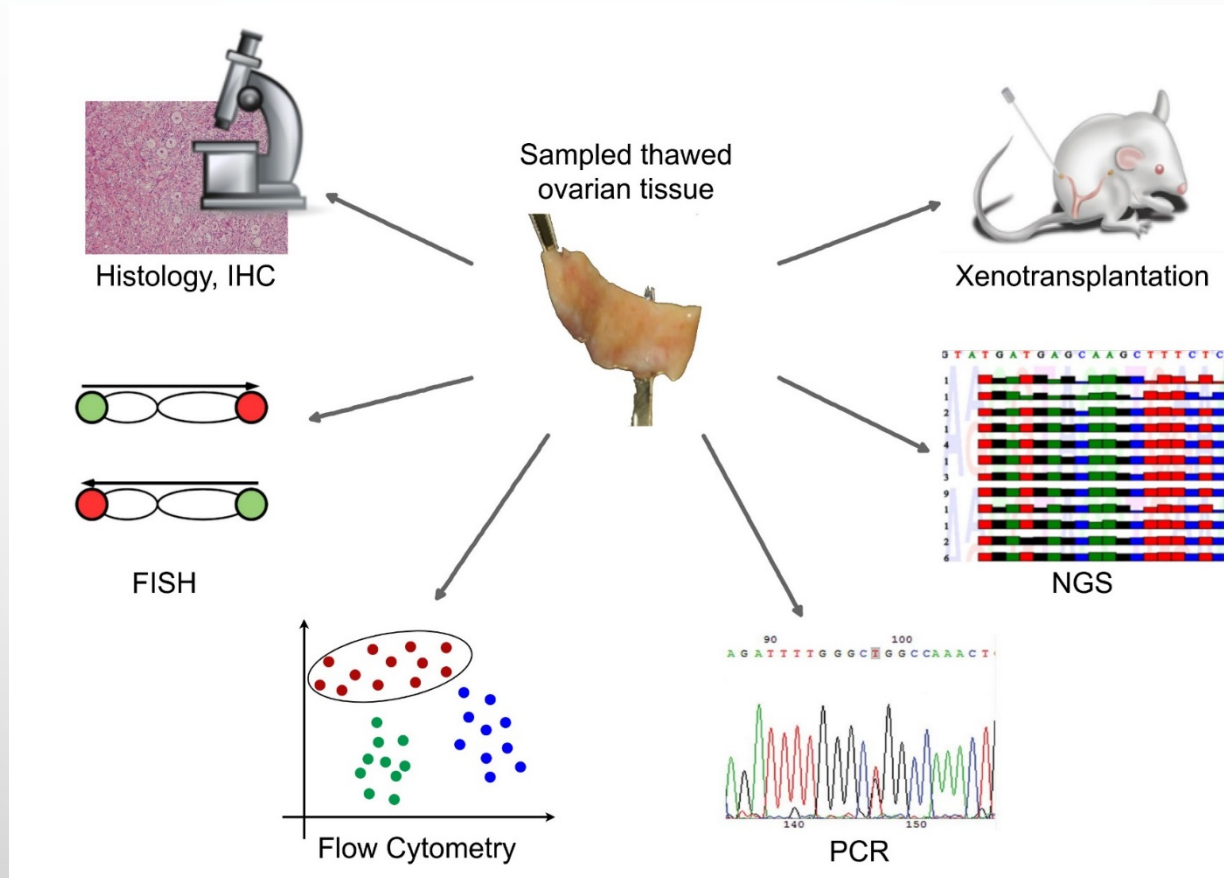
- APPEARS TO BE HIGHEST WITH LEUKEMIA
 - OVARIAN TISSUE FROM 18 PATIENTS WITH LEUKEMIA (CML OR ALL) WAS TRANSPLANTED IN MICE AND RESULTED IN TUMORS/EVIDENCE OF CANCER
- SYSTEMATIC REVIEW OF 289 STUDIES:
 - GREAT CONCERN: LEUKEMIA, OVARIAN, BRCA MUTATION
 - SERIOUS CONCERN: GASTRIC, COLORECTAL, ENDOMETRIAL
 - LESS CONCERN: CERVICAL, BREAST
 - LEAST CONCERN: LYMPHOMA



Dolmans et al. Blood 2010,
Bastings Hum Repro 2013;

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

LEUKEMIA



Shapira Moran *et.al.* Minerva Ginecol
2018

ARTICLE IN PRESS

ORIGINAL ARTICLE: FERTILITY PRESERVATION

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

^{a,b} Moran Shapira, M.D., ^{a,b} Hila Raanani, M.D., ^{a,b} Iris Barshack, M.D., ^c Ninette Amariglio, M.D., Ph.D., ^d Sanaz Derech-Haim, M.Sc., ^a Meital Nagar Marčiano, Ph.D., ^a Eyal Schiff, M.D., ^b Raoul Orvieto, M.D., ^b and ^{b1} Dror Meirow, M.D.^{a,b}

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

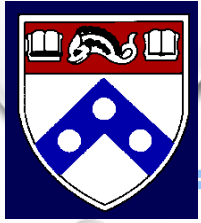


Fertility Sterility Nov 2017

Followed by Additional **spontaneous pregnancy**

2nd delivery- health baby

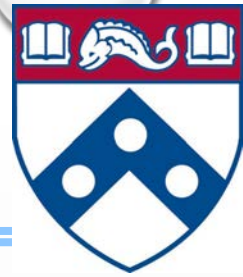
Shapira et al. 2018
Dror Meirow Slide



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



TESTIMONIAL

“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!

