Building a Family after Transplant

Celebrating a Second Chance at Life Survivorship Symposium

April 29 – May 5, 2023

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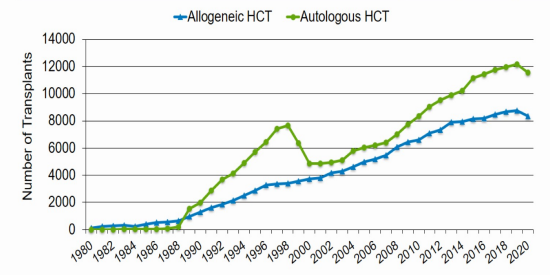
Objectives

- Describe the unique reproductive concerns for patients after bone marrow/stem cell transplant (HCT)
- Identify methods of fertility preservation prior to transplant
- Understand alternative options for family building after transplant

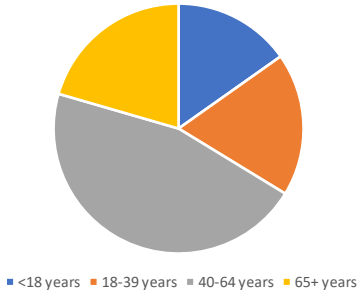
Trends in BMT in Pediatric and Reproductive Age Patients

- The number of patients undergoing HCT continues to rise
- At least a third of these patients are of pediatric or reproductive age
- With improved survival rates, future fertility is a major concern for patients

Hematopoietic Stem Cell Transplants in the US 1980-2020



Allogenic HCT in the US 2015-2020 by Recipient Age



Adapted from Center for International Blood and Marrow Transplant Research Annual Report 2021

Reproductive Challenges for Patients Facing HCT

- Conditioning regimens given prior to transplant causes germ cell loss* in the ovaries and testes
- Some fertility preservation methods require time (~2 weeks) to complete
- Patients are often balancing the acute effects of disease and complex decision-making about future quality of life

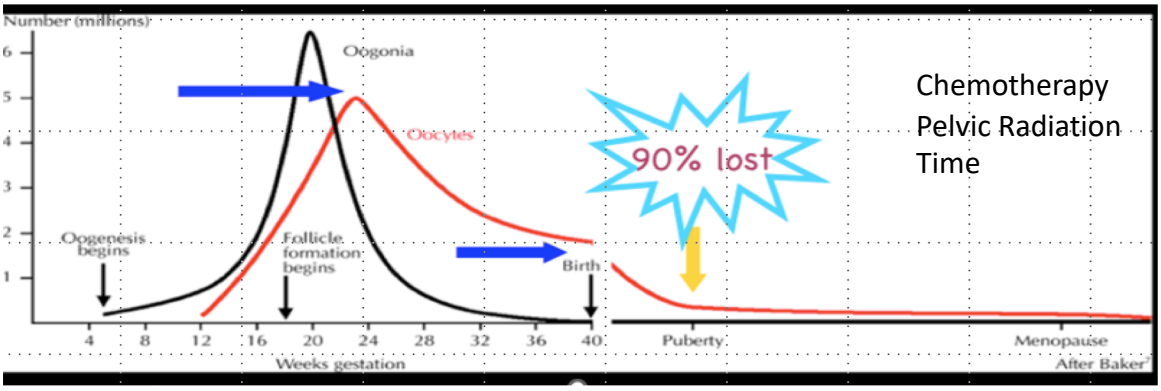
*germ cell = precursors of eggs/sperm

Factors Impacting Fertility after Transplant

- Underlying disease being treated
- Type and dose of conditioning regimen
- Recipient's age/ pubertal status
- Ovarian reserve prior to transplant (Female patients)

Female Fertility: Ovarian Reserve & The Oocyte Pool

Follicle Loss Over Time



Adapted from Speroff and Fritz. Clin Gyn End & Infert, 2005.

Pregnancy after Transplant

- <5% of transplanted individuals report having children after transplantation, but data are sparse as no established reporting guidelines
- Most of the reported cases are from patients who received cyclophosphamide conditioning alone
- With increased utilization of reduced-intensity conditioning we may see more pregnancies without assistance in the future
  - Pregnancies have been recently reported within the first 2 years after transplantation in a woman transplanted at 19 years of age after reduced-intensity conditioning

Salooja et al Lancet 2001; Borgmann-Staudt et al Bone Marrow Transplant 2012. Faraci M et al. Pediatr Transplant 2016

Pregnancy after Transplant: Potential Risks

- Increased risk of cesarean delivery, preterm delivery, and low birth weight in women who conceive after transplant
- No differences in miscarriage rates, pregnancy-induced hypertension, or birth defects
- May require multidisciplinary care with maternal fetal medicine (high-risk pregnancy) consultation

Salooja et al Lancet 2001; Borgmann-Staudt et al Bone Marrow Transplant 2012.

Options Before, and Considerations After: Planning for HCT

All adult patients and parents of pediatric patients should receive information on:

- Risk of infertility estimated according to age at transplant, previous chemotherapy and/or radiation, conditioning intensity (TBI, busulfan, alkylating agents)
- Available fertility preservation techniques
- Timelines for each technique

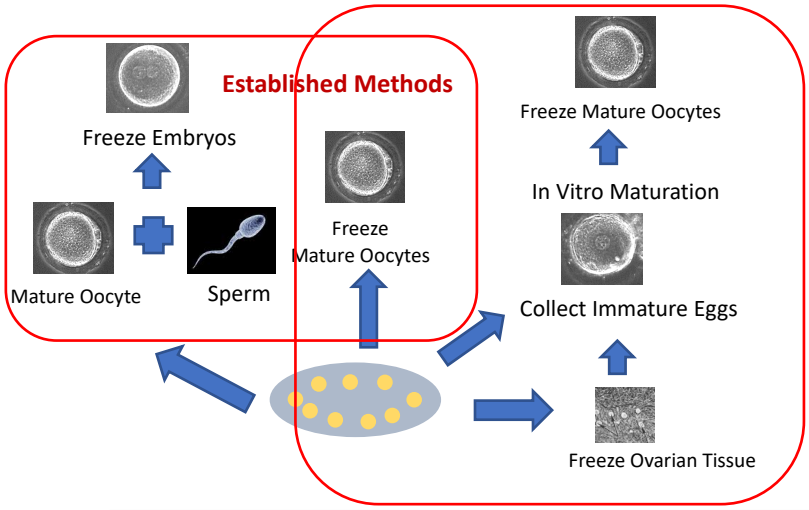
Male Fertility Preservation Options Pre-Transplant

- Sperm Cryopreservation
  - Standard of care
  - Vibratory/electroejaculatory stimulation if needed
- Testicular tissue cryopreservation
  - Prepubertal males
  - Limited Pregnancy Data

Female Fertility Preservation Options Pre-Transplant

- Oocyte Cryopreservation
- Embryo Cryopreservation
- Ovarian Tissue Cryopreservation
- Gonadotropin-Releasing Hormone (GnRH) Agonist Therapy

Female Fertility Preservation Options



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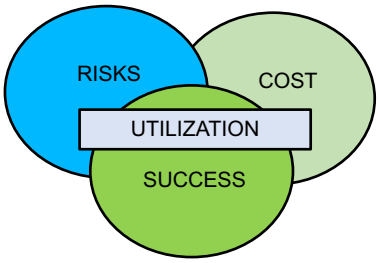
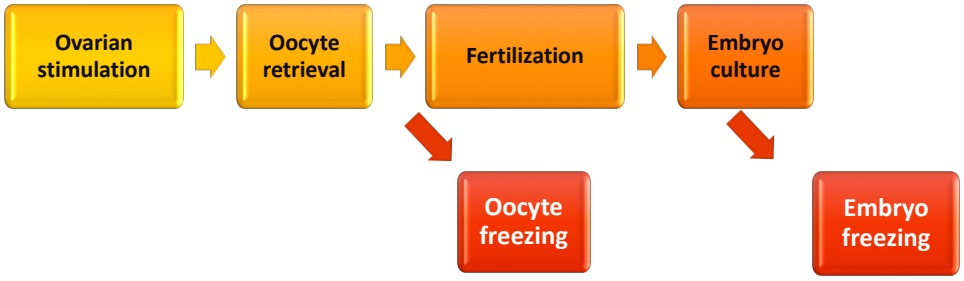
Female Fertility Preservation Considerations

- Age
- Pubertal Status
- Type of Disease and treatment planned
- Presence of partner
- Available time prior to treatment
- Health of the patient
- Willingness to use donor gametes

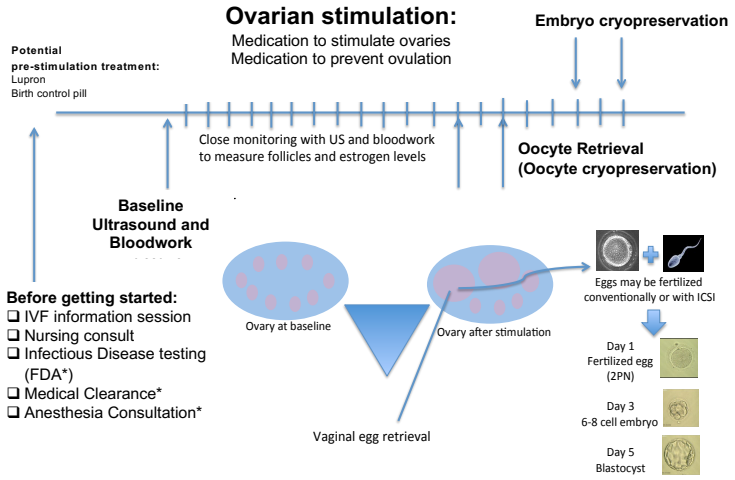


Oocyte or Embryo Cryopreservation

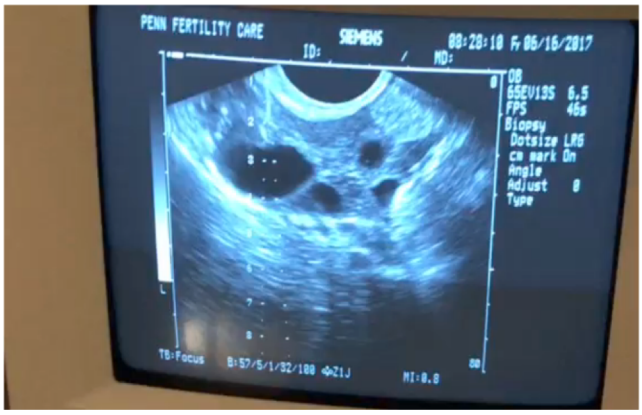


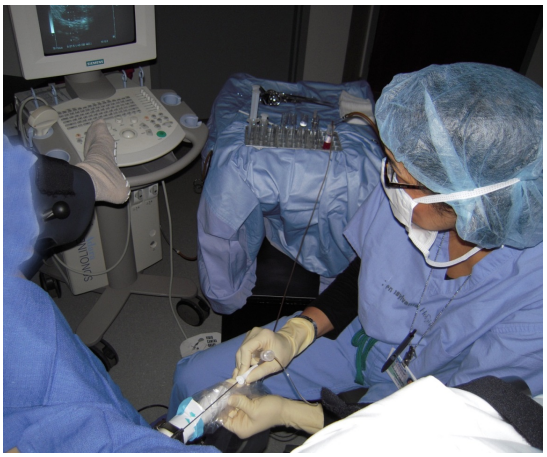
For female patients who have initiated puberty

Ovarian Stimulation Process



Oocyte (Egg) Retrieval Procedure

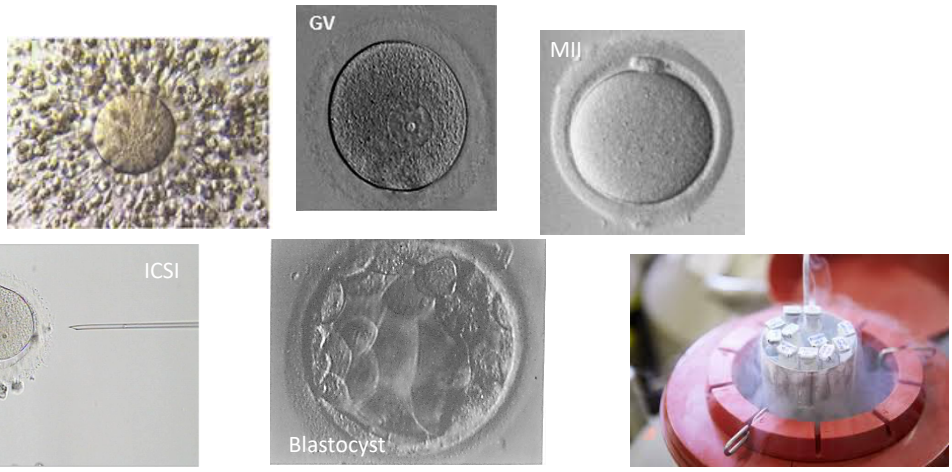




Fertilization and Embryo Culture

- The eggs are obtained, evaluated for maturity, and then they can be either cryopreserved, or inseminated with sperm to form embryos
- If fertilization is successful, the embryos will be monitored in the laboratory and frozen 5-7 days later at the blastocyst stage
- Option of pre-implantation genetic testing for genetic disorders

Laboratory Procedures



GV = germinal vesicle; MII = mature oocyte;
ICSI= intracytoplasmic sperm injection

- Oocyte and embryo banking procedures should be completed prior to initiation of gonadotoxic therapies.
- Previous chemotherapy is likely to decrease the number of retrievable eggs
- If attempted within 2-3 months of exposure, risk of no eggs retrieved at the time of egg retrieval
- Concerns that follicles recently exposed to chemotherapy may yield abnormal oocytes (animal studies)*

*Meirow et al. Hum Reprod 2001;16:632

Oocyte/Embryo Cryopreservation: Risks and Safety

- Ovarian Hyperstimulation Syndrome – 5%
  - Now avoidable with Lupron trigger*
- Ovarian Torsion < 1%
- Infection / Bleeding < 1%
- Cost: $7-20,000

The Case for Frozen Eggs: Clinical Trials of Fresh vs Frozen Oocytes

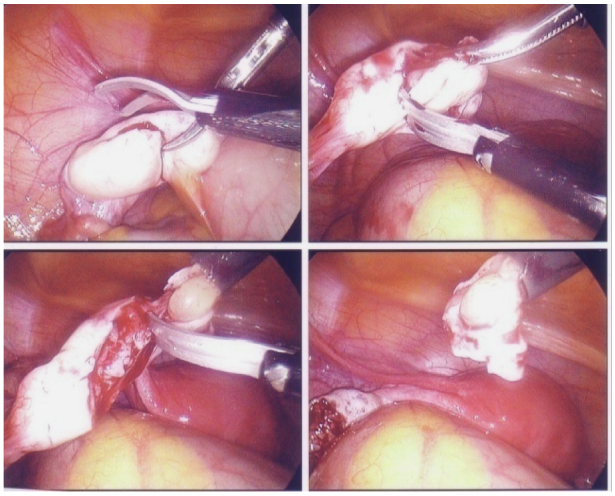
	Cobo 2008	Cobo 2010	Rienzi 2010	Parmegiani 2011
Patient population	**Oocyte donors** (n=60)	**Oocyte donors** (n=600)	Infertile pts < 43, needing ICSI with > 6 MII oocytes (n=80)	Infertile pts < 42, needing ICSI with > 5 MII oocytes (n= 31)
Mean age at retrieval	26.7±3.6	26.7±3.9	35.5±4.8	35±0.8
Implantation rate	100% fresh 40.8% frozen	40.9% fresh 39.9% frozen	21.7% fresh 20.4% frozen	NA fresh 17.1% frozen
CPR per transfer	100% fresh 60.8% frozen	55.6% fresh 55.4% frozen	43.5% fresh 38.5% frozen	13.3% fresh 35.5% frozen
CPR/oocyte thawed	6.1%	4.5%	12%	6.5%

Ovarian Tissue Cryopreservation

- No ovarian stimulation, minimal delay in treatment, no partner needed, only option in pre-pubertal girls
- Requires surgical removal of ovarian tissue, typically an outpatient procedure
- Ovarian cortical tissue removed laparoscopically, divided into small strips and frozen
- Should be considered:
  - If time does not allow for ovarian stimulation
  - Pre-pubertal girls
  - After initiation of chemotherapy

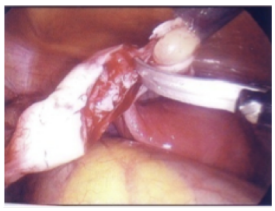
ASRM Practice Committee Opinion 2019;112:1022

Laparoscopic Removal of Ovarian Cortical Tissue

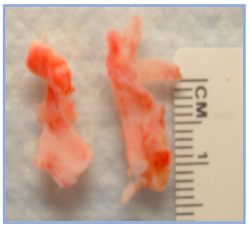


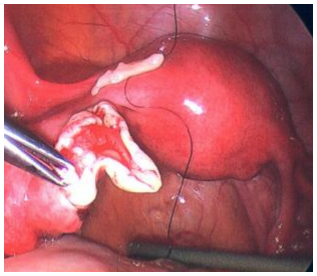
Images courtesy of C. Gracia, Penn

Ovarian Tissue Cryopreservation and Transplantation

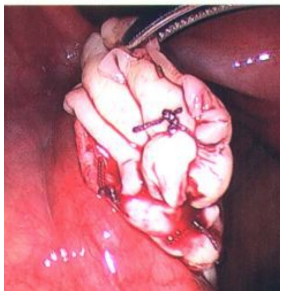


Ovarian tissue
Cryopreservation





Ovarian tissue
Transplantation



Ovarian Tissue Transplantation

- Orthotopic transplantation (contralateral ovary or ovarian fossa) most successful
  - Average time to menses 4.7 months
  - Duration of function 9-86 months
- Potential re-introduction of malignant cells into a patient in remission is a theoretical concern – leukemia, tumors with ovarian involvement
- Testing of tissue for tumor cells is possible by RT-PCR for certain tumor types
- > 150 human live births reported (live birth rate 29%)

Meirow et al. NEJM 2005;353:318, Donnez et al Fertil Steril. 2015 Nov;104(5):1097-8, ASRM Practice Committee Opinion

Ovarian Tissue Cryopreservation: Risks

- Risk of laparoscopy
- Risk of removing an entire ovary
- Multi-site retrospective chart review:
  - 43 in OTC+HCT and 99 in HCT
  - There were no clinical differences in rates of complications in girls undergoing OTC+HCT and those with HCT alone
    - 65% of patients experienced premature ovarian insufficiency with ovarian removal + HCT versus 45% with HCT alone (p=0.26)

Dwiggins et al. J of Pediatric & Adolescent Gynecology 2023

GnRH Agonist Treatment

- "Off label use" for ovarian protection prior to and throughout duration of chemotherapy
  - Decrease in ovarian activity may reduce damage to pool of immature oocytes
- Depot injection leuprolide acetate 3.75mg IM per month or 11.25 mg per 3 months
- Several randomized clinical trials (RCT) have shown mixed results
  - Meta-analysis in Hodgkin Lymphoma showed no benefit (2 RCT, 2 observational)
  - Meta-analysis in Breast Cancer showed significant reduction in chemotherapy-induced ovarian insufficiency and higher number of pregnancies (7 RCTs)

Bedaiwy et al. Fertil Steril 2011;
Munhoz et al. JAMA Oncology 2016

GnRH Agonist Treatment

- Pregnancy data not uniformly reported
- Pediatric data limited
- Experimental, remains controversial

Bedaiwy et al. Fertil Steril 2011;
Munhoz et al. JAMA Oncology 2016

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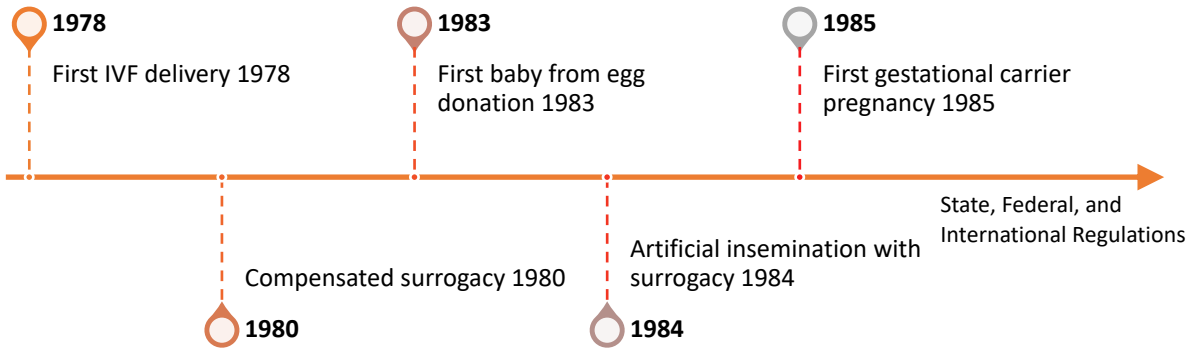
Options after Transplant: Third Party Reproduction

- Donor Eggs
- Donor Embryo
- Gestational carrier
- Adoption

Third Party Reproduction: A Brief History



Options after Transplant: Donor Egg

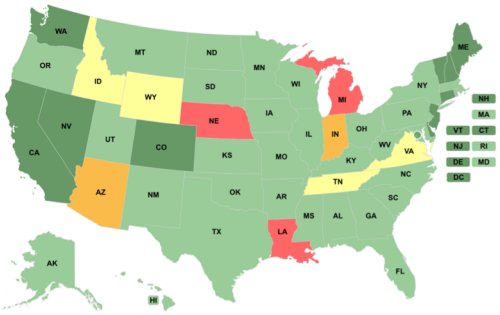
- A woman (donor) gives her eggs to another woman (recipient) to allow the recipient to have a baby
  - Can include male couples building their families using both an egg donor and a gestational carrier
- Can be non-identified (anonymous) or directed (known)
- Does not require the recipient to have a normal menstrual cycle
- Synchronized cycles versus frozen donor egg banks
- Compensation structure with variable insurance coverage

Options after Transplant: Donor Embryo

- In the current practice of in vitro fertilization (IVF), some patients may create more embryos than they need
- The extra embryos may be cryopreserved (frozen) so that they can be transferred later
- If the embryos are not used, patients have the option to donate their embryos to another patient to achieve a pregnancy
- Does not require the recipient to have a normal menstrual cycle
- Limited resource with variable success rates

Options after Transplant: Gestational Carrier

- Can be considered when medically unsafe to carry a pregnancy
- Can involve use of previously cryopreserved oocytes/embryos, or donor egg/embryos
- Availability varies by state/country



Adapted from https://www.creativefamilyconnections.com/us-surrogacy-law-map/

Family Building after Transplant: Looking Ahead

- Great strides have been made to expand the reproductive options of patients with cancer and other fertility threatening conditions
- While there are limited data in pediatric and adolescent populations to inform care, available data are encouraging
- More work is needed to study and improve safety, efficacy and the availability of these techniques for patients after transplant

QUESTIONS?

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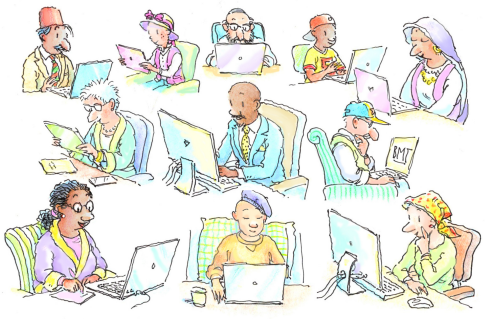
LET US KNOW HOW WE CAN HELP YOU



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