Building a Family after Transplant

Celebrating a Second Chance at Life
Survivorship Symposium

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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

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

Chemotherapy
Pelvic Radiation
Time

90% lost

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

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
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 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

**Potential pre-stimulation treatment:**
- Lupron
- Birth control pill

**Baseline Ultrasound and Bloodwork**

**Before getting started:**
- IVF information session
- Nursing consult
- Infectious Disease testing (FDA*)
- Medical Clearance*
- Anesthesia Consultation*

**Ovarian stimulation:**
- Medication to stimulate ovaries
- Medication to prevent ovulation

**Close monitoring with US and bloodwork to measure follicles and estrogen levels**

**Embryo cryopreservation**

**Oocyte Retrieval (Oocyte cryopreservation)**

**Vaginal egg retrieval**

**Eggs may be fertilized conventionally or with ICSI**

**Day 1**
- Fertilized egg (2PN)

**Day 3**
- 6-8 cell embryo

**Day 5**
- Blastocyst

Oocytes (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; MI = 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)*

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

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

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)
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)

GnRH Agonist Treatment

- Pregnancy data not uniformly reported
- Pediatric data limited
- Experimental, remains controversial
Options after Transplant: Third Party Reproduction

- Donor Eggs
- Donor Embryo
- Gestational carrier
- Adoption

Third Party Reproduction: A Brief History

- **1978**: First IVF delivery 1978
- **1980**: Compensated surrogacy 1980
- **1983**: First baby from egg donation 1983
- **1984**: Artificial insemination with surrogacy 1984
- **1985**: First gestational carrier pregnancy 1985

State, Federal, and International Regulations
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

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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