Fertility Preservation and Oocyte Cryopreservation

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Objectives
- Egg Freezing Technology
- Applications of Egg Freezing
- Fertility Preservation
- Oocyte donation

Fertility Preservation
- Defined as a variety of fertility therapies for patients anticipating medical treatment that could affect future reproductive outcomes

Egg Freezing Indications
- Fertility Preservation for Social Reasons
  - Hedge against ovarian aging
  - Uncertain relationship status
- Fertility Preservation for Cancer Patients
  - High Survivability
  - Non-estrogen dependent
  - Low recurrence risk
- Egg Banking for Oocyte Donation
- Routine IVF case management
  - Reduces ‘left-over’ embryo problem
  - Reduces ethical risk
  - Reduces legal risk

History of Cryopreservation Technology
- 2500 B.C.: Early civilizations used cryobiology and extremes of cold for medicinal purposes
- 1940s: Glycerol is discovered as a useful cryoprotectant for sperm
- 1953: First human birth from frozen sperm reported
- 1970s: Other cryoprotectants: propanediol, ethylene glycol, and DMSO minimize cellular damage during freezing
- 1984: First human birth from a frozen embryo reported
- 1986: First human birth from a frozen oocyte reported (slow freezing)
- 1993: Vitrification, EG, DMSO and Sucrose – Cryotop™

Advances in Oocyte Vitrification
Cryopreservation Techniques

Slow Freeze and Vitrification

- **Slow Freeze**
  - Lower cryoprotectant concentration
  - Longer exposure time
  - Cryomachine
  - Longer to perform
  - Technically easier

- **Vitrification**
  - Higher cryoprotectant concentration
  - Shorter exposure time
  - Shorter to perform
  - More precise timing
  - More clinical expertise
  - Open containers

Glass formation during vitrification

Vitrification: Ethyleneglycol + DMSO + 0.5M Sucrose <1 min

Equilibration: Ethyleneglycol + DMSO 10 min

MII loaded on Cryotop

Oocyte vitrification

Oocyte warming

ASRM: Egg Freezing Is No Longer Experimental
October 20, 2012

"Oocyte cryopreservation is an exciting and improving technology, and should no longer be considered experimental. Pregnancy rates and health outcomes of the resulting children are now comparable to those of IVF with fresh eggs."

The Practice Committees of the ASRM and SART, Oct 2012
Fertility Preservation in Cancer Care

Increased awareness
Earlier detection
Improved therapies

About 45% of cancer patients are now expected to survive at least 10 years, compared with 23% in the 1970s.
15% of all female cancer diagnosis are made in women under age 40

Jensen 2011

Preservation Strategies offered to Female Cancer Patients

- Gonadal medical protection
- Ovarian transposition
- Ovarian tissue cryopreservation
  - Successful reimplantation has occurred
  - Oocyte collection and fertilization has occurred
  - Few successful pregnancies yet

Preservation Strategies

- Oocyte vitrification
  - Pros:
    - Consistent results
    - Established approach
    - Success rates similar to fresh eggs
  - Cons:
    - Limited cycles
    - Pregnancy is not guaranteed
    - Ovarian stimulation needed

- Embryo cryopreservation
  - Pros:
    - Unlimited cycles
    - Could theoretically restore natural fertility
    - Could theoretically restore ovarian function
  - Cons:
    - Few pregnancies
    - Techniques still need improvement
    - Requires surgery
    - Risk of presence of malignant cells

Comparison of techniques

- Oocyte vitrification
- Ovarian tissue cryopreservation
Considerations

- Prognosis and Age
- Delay of treatment
  - Results of studies are reassuring
  - No significant delay in start of chemotherapy in breast cancer patients
- Hormone sensitive cancers
- Protocols developed to lower peak estradiol levels during stimulation
- Possibility of reseeding tumor cells with reimplantation

Limitations to Fertility Preservation In Cancer Care

- Most patients of reproductive age getting a cancer diagnosis are under extreme duress when they present for egg freezing
- Many patients cannot delay chemo or XRT safely and therefore cannot undergo ovarian stimulation and egg retrieval
- Unknown risk of ovarian stimulation to cancer prognosis
- Cost varies from $5,000.00 to $15,000.00.
  Some programs available to assist patients with financial support

Protocol for ovarian stimulation with letrozole and gonadotropins in patients diagnosed with breast carcinoma.

Clinical Applications of Egg Freezing

Egg Freezing Headlines Oct 2014

- Facebook and Apple will pay for female employees to freeze their eggs
**Trend in Delayed Childbearing**

- Average age of first-time mothers in the U.S. is rising
  - Age 21.4 yrs in 1970
  - Age 25.6 yrs in 2011
- About 20% of women in US have their first child after age 35
- 1/3 of couples in which the woman is >35 years old have infertility problems

**Fertility Preservation For Social Reasons – Data Limited**

- Best estimate is that about 800–1000 babies have been born from ‘social freezing’
- As many as 5000 cycles of egg freezing done for this reason thus far...but limited data is available
- Success rate is similar to a woman’s IVF success rate at the time of freezing
  - This success rate relies on an optimal number of oocytes cryopreserved (10–20)
- Many women presenting for this service are already over 38.
Social Freezing
Candidates for social freezing should ideally have:
- Age under 40 (38 preferable)
- Proof of good ovarian reserve
- Adequate counseling regarding available data and outcomes
- Information on freezing options
- Counseling regarding uncertain risk
- Counseling regarding alternatives
- Adoption
- Egg donation

Work-up for Fertility Preservation
- Ovarian Function
  - Day 3 FSH, AMH, Basal follicle counts
- Genetic consult/screening
  - CF, Sickle-cell, Tay-Sachs, etc.
- Infectious Diseases
  - FDA mandated-HIV, HepB, HepC, CC/Chlamydia
  - Clinic specific
- Health Screening
  - Full exam, pap/mammo up to date if indicated

From Egg Thaw to Embryo Transfer

Egg Thaw → ICSI → Fertilization Report
80% survival 65 - 75% fertilization rate

Embryo Development Timeline
- Day 1
- Day 2
- Day 3
- Day 4
- Day 5
- Day 6
- Day 7

Common Protocols For Egg Freezing
- Individualized Dosing FSH and or LH
- Egg RTR
- GnRH agonist
- CC pretreatment for 10-15 days
- hCG or agonist

Regimen for Embryo Transfer
- Recipient
- Day of transfer
- Embryo, Frozen or Thawed
- Day 1, 2, 3, 4, 5
- Frozen Eggs
- Progesterone start on the night before Egg Thaw (typically day 14 of estradiol)

Key Points for Elective Fertility Preservation
- Counseling of outcomes
- Candidacy by egg reserve and age
- Know the statistical outcomes of the ART Clinic
  - Need expertise in vitrification
  - Number of cycles completed, freeze and thaw rates, number of women who have utilized their eggs
Egg Freezing as part of Routine IVF

Can Mitigate Concerns in IVF
- Religious beliefs impact disposition of excess embryos
  - Belief systems vary
  - Patients are often uncomfortable donating embryos. What to do when family building is complete?
- Religious beliefs often do not conflict with disposing eggs
  - In cases of divorce or death of the genetic parents, embryos can become a point of contention while eggs or sperm rarely are.

Egg Donation is all around us

Egg donation history
- First successful report of egg donation—1984
- Utilized embryo capture from donor after IUI and reimplantation to the intended parent
- Used sporadically as a reproductive technique until about 1990
- First donor agencies 1990s
- First confirmed egg donation with frozen eggs—1994 (1996 in US)
- Mid 2000s, first appearance of agencies offering frozen eggs (with slow freeze)
- First US egg bank using vitrification—2008

Indications for Egg Donation
- Diminished Ovarian Reserve
- Advancing maternal age
  - Success of IVF after age 42 <5%
  - At least 80% of eggs are genetically abnormal after age 42
- Premature Ovarian failure/Menopause
  - Surgical, Genetic, after chemo
  - Unexplained
- Repetitive IVF failure
- Genetic Diseases
  - Fragile X, X-linked diseases
- Male–male partnerships
Limitations

- Donor availability
  - Ethnic background representation
- Wait Times for matching donors and recipients
- Cost of Fresh Egg donation varies by region
  - South, Midwest – approx $25,000.00
  - Northeast – approx $33,000.00
  - Far West – approx $35–40,000.00
- FDA regulations

Types of Egg Donation

- Known
  - Contracted
  - Familial
  - Altruistic
- Anonymous
  - Most common in U.S.
  - Compensated
- Semi-anonymous (brokered by agency)
  - Donor may be known to recipient but enters into contracts with intent to be compensated
  - Donor remains anonymous but is selected from an agency’s catalogue under an alias

Types of Eggs

- Fresh egg donation
  - Synchronized cycles with recipient
  - Most common in US
  - Most costly
  - Recipient accepts risks
    - Uncertain egg quality/quantity until collection
    - Donor attrition or disqualification
- Frozen egg donation
  - Slow Freeze
  - Vitrification

Comparison of techniques

<table>
<thead>
<tr>
<th>Fresh Donor Eggs</th>
<th>Frozen Donor Eggs</th>
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<tbody>
<tr>
<td><strong>Pros:</strong></td>
<td><strong>Pros:</strong></td>
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<tr>
<td>Success rates: 55–65%</td>
<td>Success rates: 65%</td>
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<tr>
<td>Recommended in severe male factor</td>
<td>Oocytes already banked, no wait for match</td>
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<tr>
<td>Often &gt;20 eggs fertilized</td>
<td>Worldwide network</td>
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<tr>
<td>Cons:</td>
<td>Cons:</td>
</tr>
<tr>
<td>Long match times</td>
<td>Often need to secure extra oocytes for sibling match</td>
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<tr>
<td>Cost 25–40K</td>
<td>Not recommended for severe male factor</td>
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<tr>
<td>Potential for high numbers of excess embryos</td>
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Lab Standards are Critical

- Vitrification ‘specialists’
  - Outcomes for each embryologist documented
  - Technicians with highest rates do all cases
- Controlled media
- Egg thaw paradigms
  - Proven donors – thaw 4–6 eggs/case
  - New donors – thaw 6/case
- All ICSI
- Codification of High Quality Embryos (HQE)
  - Defined grade A, B
  - Blastocyst ratings

Pilot Oocyte Vitrification Program: 2006–2007 at RBA

- Pilot program using vitrification in egg donation sponsored by pharma
- Highly selected donors and recipients
- Single donor management protocol
  - Antagonist based, FSH only, hCG trigger
- Single replacement protocol
  - Agonist down–reg/Oral Estradiol/Injectible P4
  - No severe male factor
  - No severe uterine factor/RPL
First 20 Egg Thaws at RBA

- Thaw: 155 (7.7/recip)
- Survived: 135 (87%)
- Fertilized: 117 (86%)
- Blastocysts-d5: 85 (73%)
- No of Es for ET: 47 (2.4/Recip.)
- No of Embryo Cryo/: 31 (1.5/Recip.)

Results: 85% Live Birth Rate (17/20)

Nagy et al 2008 Fertility and Sterility

MyEggBank.Com

- Separated from RBA in 12/2010
  - Currently without its own inventory
  - Core partnerships
    - Seattle Reproductive Medicine
    - Reproductive Science Center of New England
    - Center for Reproductive Medicine-Orlando
    - Reproductive Biology Associates-Atlanta
  - Contracts with outside clinics
    - 60 + affiliated practices
    - Tech
    - Non-tech

MEB-NA

On-line gateway to matching

Frozen Donor Oocyte Fertilization

- Egg Thaw (6-8 eggs)
- ICSI
- Fertilization Report
- 80% survival
- 65–75% fertilization rate

Embryo Development Timeline

Embryo Transfers done at blastocyst stage (day 5)

Single Blastocyst success rate: 65%

Single embryo transfer

Strongly recommended

Recipient

Date of Embryo

Embryo Transfer on Day 5

Lupronide Acesate

Programme

Frozen Eggs

Progestrone start on the night before Egg Thaw
(typically day 14 of estradiol)
MEB–NA Statistics

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<tr>
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<th>Traditional Fresh Egg Donation</th>
<th>My Egg Bank frozen donor eggs</th>
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<tbody>
<tr>
<td>Average pregnancy rate</td>
<td>55%–60%</td>
<td>65%</td>
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<tr>
<td>Average time to complete treatment</td>
<td>up to one year or more</td>
<td>1 to 3 months</td>
</tr>
<tr>
<td>Average cost of one donor cycle</td>
<td>$26,000 – $44,000</td>
<td>$17,000 – $20,000</td>
</tr>
<tr>
<td>2,300+ cycles completed</td>
<td>55%–65% pregnancy rate*</td>
<td>1,000+ ongoing or delivered</td>
</tr>
<tr>
<td>Cumulative expectation of pregnancy per patient</td>
<td>80%–85%</td>
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Guarantee Programs offered by MyEggBank

- **Guarantees**
  - 2 HQE
    - Guarantees at least 2 HQE. If no pregnancy AND less than 2 HQE, patient gets a freebie cycle
  - 18 K
- **Frozen Egg Advantage**
  - Flat fee (28 K) with live birth guarantee.
  - Up to five egg thaws and all transfers available from the 5 thaws

Conclusions

- Technology is currently expanding
  - Reproductive options
  - Reproductive autonomy
- Data on outcomes is limited to the novelty of the technology
  - Future outcomes data will continue to inform us
    - Birth outcomes
    - Safety
    - Social impact

Conclusions

If safe and applicable, fertility preservation options should be offered to cancer patients

Oocyte vitrification is a safe and effective method

Applications of oocyte vitrification are diverse:
  - Fertility preservation
  - IVF
  - Oocyte donation

Acknowledgements

- Dr. Daniel Shapiro
- Dr. Z Peter Nagy
- Dr. Andrew A Toledo
- Dr. Carlene W Elsner
- Dr. Dorothy Mitchell–Lee
- Dr. Robert J. Straub
- Dr. Scott M Slayden
- Graham Wright
- Jeremy Chang
- Thomas Elliot