Ovarian cortical biopsy for fertility preservation

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Financial Disclosure

- I have no financial relationships to disclose
Objectives

• Review current state and indications for pediatric and AYA ovarian tissue cryopreservation
• Outline surgical techniques and freezing process for cortical biopsies
• Compare cortical biopsy vs oophorectomy for FP in pediatric and AYA patients
• Demonstrate reimplantation using minimally invasive techniques
Case Presentation

Fertility preservation consult:

6 year old female with aplastic anemia pending HSCT
Childhood cancers

• In 2018, >15,000 children in the United States <19yo were diagnosed

• Survival is improving!
  – 1970s- 5-year survival rate of ~ 60%
  – 2010s- > 80% survive > 5 years after diagnosis
    • 400k survivors in the US today

• Late effects
  – Infertility

Pediatric OTC

• Efficient method to preserve thousands of follicles
  – Malignant / non-malignant indications
  – Concern for reintroduction of cells

• Prepubertal
  – IVF and ovarian stimulation may not be possible
  – Concomitant surgical procedure

• Pubertal
  – IVF and ovarian stimulation may not be desirable, affordable or expedient
COMING SOON!

ASRM to lift “experimental” designation of OTC

Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama
Access to OTC in pediatric/AYA pts

• Adolescents may feel uncomfortable discussing:
  – Infertility
  – Early menopause
  – Sexual function

• In children, it may be many years before these conversations would need to take place
  – Children may have limited understanding regarding reproduction and sexual function

• Ethical considerations (prognosis, posthumous)
## Selection for OTC

### EDINBURGH CRITERIA?

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
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<tbody>
<tr>
<td>Age younger than 35 years</td>
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<td>A realistic chance of surviving for five years</td>
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<td>A high risk of premature ovarian insufficiency (&gt;50%)</td>
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<td>No previous chemotherapy or radiotherapy if aged 15 years or older at diagnosis; Mild, non-gonadotoxic chemotherapy acceptable if younger than 15 years</td>
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<td>Informed consent (from parents and, where possible, patient)</td>
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<td>Negative serology results for human immunodeficiency virus, syphilis, hepatitis B</td>
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<td>Not pregnant and no existing children</td>
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Unanswered questions

• *Cortical biopsy vs oophorectomy?*
  – *How much tissue is needed to achieve a successful live birth?*

• What is the best surgical method to procure and reimplant the tissue?

• What is the best system and location to deliver the tissue?

• What is the best method of cryopreservation (slow freeze or vitrification)?
Current state of OTC

- First livebirth in 2004
- Now > 150 livebirths worldwide from orthotopic tissue reimplantation
- Only offered in the United States under IRB approved registries

Current state of OTC

• Birth outcomes
  – Almost half become pregnant and 1/3 achieve LB
  – Most success is from adult women

• 2009 systematic review
  – 1000 pts (0.4-20.4 years)
  – 18 transplanted with autologous tissue <21yo - 10 LB

• First live birth from prepubertal child (14yo) in 2015- now 9yo

• Van der Ven H, et al.. Human reproduction. 2016;31(9):2031-2041
• Corkum KS et al, Journal of Pediatric Surgery. 2019
Current state of OTC
Limitations of OTC

• Only 2 livebirths yet reported from tissue frozen in prepubertal girls
• No livebirths from heterotopic reimplantation
  – 2 livebirths from peritoneal implantation
• Currently not indicated for induction of puberty or long term endocrine restoration
  – Graft longevity MAX up to 7 years
Ovarian cortical biopsy technique
Ovarian cortical biopsy technique
Why cortical biopsy vs oophorectomy?

- Ease of tissue dissection and preparation
- More anatomic site for reimplantation
- Paucity of data on efficacy in prepubertal girls
- Leaves more native ovary if residual function is achieved
- Less potential for ureteric injury
Ease of preparation
Ovarian Re-implantation:
Ovarian Medulla Present
Tissue spread within peritoneal pockets?
Tissue spread within peritoneal pockets?

Courtesy of Dr. Donnez
Peritoneal window
Sheep model for OTC

• 6 ewes underwent 18 procedures
  – Recovery / freezing of ovarian cortex
  – Thawing / orthotopic regrafting of cortex
  – Retrieval of transplanted tissue
• IHC staining with CCASP3 and CD31 apoptosis markers at each stage
• We were unable to retrieve tissue for sufficient analysis from peritoneal pockets due to spread

Davis & Flyckt et al., 2019 (in preparation)
Sheep model for OTC

Davis & Flyckt et al., 2019 (in preparation)
Residual ovarian function after HSCT

- **Allogeneic:** 14-25% recovery of ovarian function
  - Young, no total body irradiation
- **Autologous:** A study of 17 women who underwent autologous SCT showed that five (29%) recovered their ovarian function and that the recovery rate for women younger than 25 years was 79%

Ureteric injury at pelvic brim

- Uterosacral ligaments
- Pelvic brim
- Crossing of uterine artery
- Tunnel of Wertheim
- Near the uretero-vesical junction
Case Presentation

Fertility preservation surgery in 6yo:

• Combined with port placement
Case Presentation
Reimplantation
Optional slide: In vitro maturation of immature oocytes

- Experimental, live birth rates are still low
- Could be used with or without frozen ovarian tissue
- 2014- first live birth from a patient who underwent oophorectomy for ovarian cancer using IVM from frozen ovarian tissue
  - Proof of concept
  - Reduce risk of malignant contamination with autotransplantation
Discussion

• In reality, I do typically take ovary in young girls (SIZE)
• Potential for IVM from ovarian tissue? If so, need more tissue...
• Other factors
  – Prior chemotherapy and planned chemotherapy- how likely is POI?
  – How sick is the patient- if I have to get in and out or if platelets are low, oophorectomy is easier and faster
  – Surgeon comfort/skill
  – History of prior ovarian surgery
  – Is ovarian transposition or other surgeries planned that will alter pelvic anatomy
  – Guided discussion with family and child if possible