Transitional Urology: Optimizing Care for Adolescents and Adults with Pediatric-Onset Urologic Conditions

Michael Hsieh, MD, PhD
Spina Bifida Survival: a Medical Triumph

Survival to 30s

0% 20% 40% 60% 80% 100%

1960s 2014
It’s Not Just Spina Bifida
(Most) Adults are Not Big Children
Who Will Take Care of Jenny As She Gets Older?

Born with spina bifida
VP shunt
Spina bifida closure

Shunt revisions
Bladder augmentation
Mitrofanoff

Needs cancer surveillance
Mitrofanoff stenosis
Needs C-section for pregnancy
Pediatric and “Adult” Urologists
Challenges of Transitional Care
Urology-Specific Challenges of Transitional Care
Urology-Specific Challenges of Transitional Care
This is an Ongoing, National-Level Discussion

Research Needs for Effective Transition in Lifelong Care of Congenital Genitourinary Conditions

February 2, 2015
Lifelong Urologic Care - Conceptual Framework

Congenital
- Spina Bifida
- Ureteral/Urethral Abnormalities
- Epispadias/Exstrophy
- Disorders Sexual Differentiation

Acquired
- Trauma
- Cancer
Lifelong Urologic Care
Conceptual Framework

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Neuro-Cognitive

Bladder/Bowel

Renal

Sexual Function/Fertility/Body Image

SYSTEMIC
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Research Domains
- Epidemiology
- Outcomes
- Clinician-Directed Care
- Self-Management
- Systems Issues

Brain Function/Fertility/Body Image

Sexual

SYSTEMIC

Bladder/Bowel

Renal
What Should We Be Doing to “Transition” Our Patients?

Recommended Health Care Transition Timeline

AGE: 12  
Make youth and family aware of transition policy

AGE: 14  
Initiate health care transition planning

AGE: 16  
Prepare youth and parents for adult model of care and discuss transfer

AGE: 18  
Transition to adult model of care

18-22  
Transfer care to adult medical home and/or specialists with transfer package

23-26  
Integrate young adults into adult care

Gottransition.org
Transitional Urology: a Joint Children’s-GW Venture

The Clinic for Adolescent and Adult Pediatric Urology (CAPITUL)
CAPITUL

• First dedicated transitional urology program in the mid-Atlantic region
• Will also see adults with pediatric onset urologic disorders
• Interface closely with other regional medical centers and practices (think Maryland!)
Patients to Date – Challenging!

• 19 yo man with multiple urethrocutaneous fistulas after failed hypospadias repairs
25 yo woman with cloacal extrophy and continent urinary diversion with UTI and stones
25 yo woman with cloacal exstrophy and continent urinary diversion with UTI and stones
Challenging Patient #3

- 25 yo man with spina bifida with incontinence and urethral erosion from indwelling catheter

Appendicovesicostomy created and maximal anticholinergic rx – pt now continent!
Cancer Survivorship

Five year relative survival rates

Year


ALL

AML

Kersey, John, H. 1997, Blood
Fertility Effects of BMT on Adolescent Boys

- 68 boys >12 yo (2003-2010)
- 6 tried sperm banking pre-rx
- 33 tried banking pre-BMT (39% azoospermic, 15% oligospermic)

Nahata et al., Pediatr Blood Cancer 2013
Fertility Preservation Preferences and Perspectives Among Adult Male Survivors of Pediatric Cancer and Their Parents

Daniel M. Stein, MD, MHS,1,2 David E. Victorson, PhD,2,3 Jeremy T. Choy, MD,1 Kate E. Waimey, PhD,4,4* Timothy P. Pearman, PhD,2,3 Kristin Smith,4 Justin Dreyfuss,1 Karen E. Kinahan, MS, RN,3 Divya Sadhwani,5 Teresa K. Woodruff, PhD,4 and Robert E. Brannigan, MD1,4

Special thanks to Shana Jacobs
Critical Review of Clinical Practice Guidelines for Fertility Preservation in Teenagers and Young Adults with Cancer

Adam D. Jakes, MBBS, MSc, Perrine Marec-Berard, MD, Robert S. Phillips, MA (Cantab), BM BCh (Oxon), PhD, and Daniel P. Stark, MB BChir, PhD

Take home messages:
Guidelines vary widely in recommendations
All guidelines recommended sperm banking by postpubertal boys

**ASCO 2013:** if boys can’t produce semen, epididymal/testicular aspiration/biopsy. Testicular shielding during XRT, testicular tissue preservation supported in trial setting. GnRH analogs mentioned but not supported

**AAP 2008:** in addition to above, electroejaculation & post-masturbation urine are options, testicular tissue preservation not recommended

Special thanks to Shana Jacobs
<table>
<thead>
<tr>
<th>Option</th>
<th>Sperm Banking (Injection)</th>
<th>Sperm Banking (Alternative Collection Methods)</th>
<th>Radiation Shielding of Genitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Status</td>
<td>Standard</td>
<td>Experimental</td>
<td>Standard</td>
</tr>
<tr>
<td>Definition</td>
<td>Sperm obtained through masturbation, then frozen</td>
<td>Sperm obtained through testicular extraction or electroejaculation under sedation</td>
<td>Use of shielding to reduce the dose of radiation delivered to the testes</td>
</tr>
<tr>
<td>Pubertal Status</td>
<td>After puberty</td>
<td>After puberty</td>
<td>Before and after puberty</td>
</tr>
<tr>
<td>Time Requirement</td>
<td>Outpatient procedure</td>
<td>Outpatient procedures</td>
<td>In conjunction with radiation treatments</td>
</tr>
<tr>
<td>Success Rates</td>
<td>Generally high</td>
<td>If sperm is obtained, similar to standard sperm banking</td>
<td>Possible with select radiation fields and anatomy</td>
</tr>
<tr>
<td>Cost</td>
<td>Approx. $1,500 for 3 samples; storage fees average $500/year</td>
<td>Varies greatly based on collection method</td>
<td>Generally included in the cost of radiation treatments</td>
</tr>
<tr>
<td>Timing</td>
<td>Before treatment</td>
<td>Before treatment</td>
<td>During treatment</td>
</tr>
<tr>
<td>Special Considerations</td>
<td>Deposits can be made every 24 hours</td>
<td>Can be considered if male cannot ejaculate</td>
<td>Expertise required; does not protect against affects of chemotherapy</td>
</tr>
</tbody>
</table>

Fertile Hope
<table>
<thead>
<tr>
<th>Testicular Tissue Freezing</th>
<th>Testicular Sperm Extraction</th>
<th>Donor Sperm</th>
<th>Adoption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>Standard</td>
<td>Standard</td>
<td>Standard</td>
</tr>
<tr>
<td>Tissue obtained through biopsy and frozen for future use</td>
<td>Use of biopsy to obtain individual sperm from testicular tissue</td>
<td>Sperm donated by a man for artificial insemination or IVF</td>
<td>Process that creates a legal parent-child relationship</td>
</tr>
<tr>
<td><strong>Before and after puberty</strong></td>
<td><strong>After puberty</strong></td>
<td><strong>After puberty</strong></td>
<td><strong>After puberty</strong></td>
</tr>
<tr>
<td>outpatient procedure</td>
<td>outpatient procedure</td>
<td>readily available for purchase</td>
<td>Varies depending on the type of adoption</td>
</tr>
<tr>
<td>No available human success rates</td>
<td>30.70% in post-pubescent patients</td>
<td>50-80%</td>
<td>N/A</td>
</tr>
<tr>
<td>$500-$2,500 for surgery; $300-$1,000 for freezing; $500/year for storage</td>
<td>$4,000-$16,000 (in addition to costs for IVF)</td>
<td>$200-$500 per vial (in addition to costs for IUI or IVF)</td>
<td>$2,500-$35,000</td>
</tr>
<tr>
<td>Before treatment</td>
<td>Before or after treatment</td>
<td>After treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>May be only option for pre-pubescent boys</td>
<td>Center should be able to freeze sperm found at time of biopsy</td>
<td>Can choose donor based on wide range of characteristics</td>
<td>Medical history often a factor</td>
</tr>
</tbody>
</table>

Fertile Hope
Testicular Biopsy and Microsurgical Epididymal Sperm Aspiration (MESA)
Testicular Tissue Cryopreservation for Fertility Preservation in Patients Facing Infertility Causing Diseases or Treatment Regimens

Hermann and Orwig (Eds) “Male Germline Stem Cells: Developmental and Regenerative Potential”, Springer 2011
Standard and Experimental Methods for the potential use of cryopreserved testicular tissue

Clark et al., Nat Med 2011; Valli et al., Fertil Steril 2014
Challenges to SSC transplantation for cancer survivors

- Majority of patients are not informed about fertility risks and options for preserving fertility
  - Multidisciplinary discussions
- Small biopsies from prepubertal patients may contain few stem cells
- Timing for reintroducing SSCs back into patients
- Malignant contamination in testicular biopsy
- Optimize cryopreservation
  - Cell suspension versus tissue
  - Slow freeze versus vitrification

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC
Testicular Tissue Cryopreservation Study

Eligibility:
-Male of any age scheduled for treatment with risk of causing permanent and complete loss of subsequent testicular function.

-For subjects ≥18 years old, eligibility is limited to high and intermediate risk patients
-For subjects <18 years old, eligibility is limited to high risk patients

“Piggyback” onto anesthesia given for bone marrow biopsies, line placement, etc.

High Risk: ≥80% risk of prolonged azoospermia by Fertile Hope criteria
Intermediate Risk: 21-79% risk
# Assessing Infertility Risk

<table>
<thead>
<tr>
<th>Degree of Risk</th>
<th>Treatment</th>
<th>Common Usage</th>
</tr>
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<tbody>
<tr>
<td><strong>High Risk</strong></td>
<td>Prolonged azoospermia post-treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Total body irradiation (TBI)</strong></td>
<td></td>
<td>Bone marrow transplant/stem cell transplant (BMT/SCT)</td>
</tr>
<tr>
<td><strong>Testicular radiation dose &gt; 2.5 Gy in men</strong></td>
<td></td>
<td>ALL, NHL, sarcoma, germ cell tumors</td>
</tr>
<tr>
<td><strong>Testicular radiation dose ≥ 6 Gy in boys</strong></td>
<td>Protocols containing procarbazine: COPP, MOPP, MVPP, CHVPP, CHVPP/EVA, MOPP/ABVD, COPP/ABVD</td>
<td>BMT/SCT</td>
</tr>
<tr>
<td><strong>Alkylating chemotherapy for transplant conditioning (cyclophosphamide, busulfan, melphalan)</strong></td>
<td>Any alkylating agent (e.g., procarbazine, nitrogen mustard, cyclophosphamide) + TBI, pelvic radiation, or testicular radiation</td>
<td>Sarcoma, NHL, neuroblastoma, ALL</td>
</tr>
<tr>
<td><strong>Cyclophosphamide ≥ 7.5 g/m²</strong></td>
<td>Cranial/brain radiation ≥ 40 Gy</td>
<td></td>
</tr>
</tbody>
</table>
Study Details

• Inclusion Criteria:
  • Male of any age
  • Scheduled to undergo treatment for the treatment or prevention of a medical condition or malignancy with risk of causing permanent and complete loss of subsequent testicular function.
  • Newly diagnosed or recurrent disease
  • Approved for wedge biopsy or orchiectomy
  • Cryopreservation of testicular tissue pieces by slow freezing method (5% DMSO)
  • A small portion of the tissue will be allocated to research (max. 25%) and stored at Magee-Womens Research Institute
  • 75% of the tissue for future patient use
  • Long-term storage at Reprotech Ltd., Roseville, MN
TTC- Coordinating Center

Recruitment Site

- Determine Eligibility
- Informed Consent
- Send blood and urine samples Memorial Blood Centers (MBC)
- Send paperwork and MBC lab results to Reprotech
- Send de-identified testicular tissue and plasma to CC

Memorial Blood Centers
- Blood and FDA specimen testing
- Long term storage site of patient tissue

Reprotech Ltd.
- Lab work (1 serum, 2 plasma, urethral swab or urine)
- Testicular tissue, 1 plasma
- Patient tissue, 1 plasma

Reprotech Agreement, Memorial Blood Centers lab results

TTC – Coordinating Center
Research Goals

- Optimize techniques for cryopreservation of testicular tissue
- Optimize methods for SSC transplantation
- Assess malignant cell contamination in harvested patient testicular tissue
- Develop methods for removing contaminating cancer cells in testicular tissue.
- Develop strategies to isolate/enrich the spermatogonial stem cell
- Establish culture conditions for *in vitro* expansion of human SSCs
- **Testicular xenografting**
Financial Assistance

- Insufficient insurance coverage

- Verna’s purse in association with Reprotech offers discounted storage fees

- Participation in research studies to cover costs for tissue freezing and cryopreservation
Patients Already Being Recruited/Approached

• 17 yo boy with hepatosplenic T cell lymphoma about to undergo BMT – testicular tissue harvested
Help is on the Way

• Kelly Chiles, GW andrologist
Oncofertility Conclusions

• We are excited to offer the potential for fertility preservation to boys undergoing gonadotoxic therapy for cancer

• Thank you for your support of the program – you will help enable today’s children to be tomorrow’s parents!
The Broader Need

• Sally Evans – Spina bifida/PMR
• Jeff Dome - Oncology
• Jennifer Dean - Oncology
• Lisa Tuchmann – Adolescent Medicine
• April Barbour – Internal Medicine
• Tova Ronis - Rheumatology
• Barbara Speller-Brown – Sickle Cell
• Veronica Gomez-Lobo - Gynecology
• Judy Liu and Henry Kaminski - Neurology
• Christian Nagy - Cardiology
• Pam McClain
The Solution

• Umbrella program with pool of dedicated:
  – Social workers
  – Nutritionists
  – Psychologists
  – Physical therapists
  – Patient navigators
  – Research coordinators

• Tremendous philanthropic potential
• Clearinghouse for transition policy guidelines, databases of adult regional caregivers
• Potential for transitional care fellowship
• Cost savings and increased clinical volume
• Higher quality patient care
Implementation Timeline

2014-May 2015: Urology rollout

May 2015-May 2016: Expansion to new programs

May 2016-: Strengthening of existing and new programs
Transitional Medicine and Surgery (TRAMS) at GW
Acknowledgements

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• Kyle Orwick
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• Cath Bollard