Uterus Transplant

7/8/14

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CREOG objective

• 5. (REI) IV. (Infertility) C. (Ethical considerations)
  • Describe the ethical implications surrounding fertility treatment. (MK, P, ICS)
  • Describe the health care resource allocation concerns pertaining to diagnosis and treatment of infertility. (MK, P, ICS)
Uterine Factor Infertility

- Absolute vs relative
- Congenital vs acquired
Gestational Carrier

• Technically straightforward
  – Emotionally, socially, legally less so
• Opposed by some religions, illegal in some countries, many countries silent
  – Gestational mother = legal mother some places
• Who has control and decision-making
  – No physical control
Gestational Carrier – ASRM opinion

- Informed consent: risks
- Psych evaluation and counseling
- Independent legal counsel
- Reasonable economic compensation
Ethics of Uterus Transplant

• Apr 2000 Saudi Arabia
• 2009 FIGO Guidelines
• Aug 2011 Turkey
• Dec 2011 Indianapolis Consensus
• Sep 2012-Apr 2013 Sweden
• 2012-2013 Montreal Criteria for Ethical Feasibility of Uterus Transplantation
Montreal Criteria for the Ethical Feasibility of Uterine Transplantation

• Established in 2012, updated 2013
• If UTx => viable gestation, medically safe for mother and fetus, woman may be candidate if criteria met for 1. recipient 2. donor 3. health care team.
Montreal...1. The recipient

- Genetic female*, reproductive age, no medical contraindications to transplant
- Documented congenital or acquired UFI has failed gold standard tx and conservative therapy
- Personal or legal contraindication to surrogacy and adoption measures OR seeks to experience gestation
- No psych comorbidity, decision for UTx not irrational.
- Not unsuitable mother
- Likely to take antirejection meds and followup
- Can make informed decision/consent.
Montreal...2. The donor

• Female of reproductive age, no med contraindications to donation
• Insists doesn’t desire more parity OR signed advanced directive for postmortem donation
• No h/o uterine damage or disease
• No coercion, can make informed decision/consent
Montreal...3. The health care team

- Institution meets Moore’s 3rd criterion for institutional stability
- Provides adequate informed consent both parties: risks, sequelae, chances of success and failure
- No conflict of interest
- Duty to preserve anonymity if not explicitly waived
Human Uterus Transplant

• Apr 2000 Saudi Arabia
  – 2002 Int J Cynaecol Obstet
  – 16 baboon and 2 goat orthotopic autografts *

• Aug 2011 Turkey
  – 2013 Fertil Steril
  – No prior related research

• Sep 2012 - Apr 2013 Sweden (n=9)
  – May 2014 Fertil Steril
Human UTx – preparatory research

• Brannstrom et al (Sweden)
  – >10 years research on animal models: rodents, large domestic animals, nonhuman primate
  – >23 original research papers
  – 5 PhD theses

• [http://youtu.be/kxhl2TPIUJk](http://youtu.be/kxhl2TPIUJk)
  – (Mats Brannstrom at COGI; 27:38)
Definitions - grafts

- Auto – same individual
- Syn – genetically identical
- Allo – genetically non-identical, same species
- (Xeno – different species)
- Heterotopic – abnormal location
- Orthotopic – normal location
Animal research

MODELS
• Mouse
• Rat
• Rabbit
• Sheep
• Pig
• Goat
• Rhesus macaque
• Baboon
• Cynomolgus monkey

AREAS OF RESEARCH
• Vascular anastamososes/surgical technique
• Ischemia-reperfusion injury
• Immunosuppression and rejection
• Pregnancy and live birth
Mouse

- First model in Sweden group
- Mostly syngeneic, heterotopic

Figure 7. A spontaneous delivery from the transplanted uterus through the stoma. The tail of the fetus is visible.
Rat

- Allogeneic, orthotopic, immunosuppression, pregnancies/LB
# Sheep

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Pregnancy in 3/5, 1 uterine torsion with IUFD twins, day 88 pregnancy normal at c/s, term pregnancy normal at c/s.

5/12 good allografts, 3/5 pregnant with ET, 1 ectopic, 1 pregnancy to 105 days, 1 c/s at term of viable lamb.

https://www.youtube.com/watch?v=dvIsZz7kqa0
Human Research

• 2007 of 150 multi-organ donors, **9 consented to uterus retrieval**. 8 retrieved. 2 included entire length of artery and vein to common iliac origin, 2 had unilateral loss of uterine vessels. Bx/histology of 1 s/p 12 hrs cold ischemia showed no e/o morphologic changes.

• 2012 at radical hysterectomy, uterine arteries and veins dissected separately and lengths measured (mean ~70 mm). MRI compared to actual lengths ok. Perioperative and postoperative morbidity not different compared to control radical hyst.
Human UTx – Saudi Arabia

• Donor & recipient
  – Live donor: 46 yo G? hyst for benign ovarian tumor
  – Recipient: 26 yo G1 peripartum hyst for PPH

• Surgical technique/vascular anastamoses
  • Saphenous veins grafts, anastamosed to external iliacs.
Human UTx – Saudi Arabia

• Function
  – Estrogen(progesterone x 3 months, +2 withdrawal bleeds.

• Morbidity
  – Laceration in donor’s left ureter found at initial surgery; repaired by urologist
  – 99th day, dusky cervix prolapsing into vagina with foul-smelling discharge. At hysterectomy, uterus infarcted, uterine arteries, veins, saphenous grafts thrombosed. Histo: tubes viable, absence of rejection.
Human UTx – Turkey

• Donor & recipient
  – Deceased 22 yo G0 multi-organ donor
  – Recipient: 21 yo MRKH w/ best HLA match (of 3)

• Surgical technique/vascular anastamoses
  – End-to-side vascular anastamoses to external iliacs.
UTx – Turkey

• Function
  • Menstruation 20 days after procedure, then estrogen/progesterone 5 months, then spontaneous.
  • 2 pregnancies:
    – 1 biochemical
    – 1 early Sab (no FCA) w/ D&C (46 XX, didn’t rule out contamination).
    – 8 grade I, d3 embryos from 2 cycles prior to transplant

• Morbidity
  • No complications reported
Human UTx – Sweden (n=9)  
Donors & Recipients

• Live known donors (5 recipients’ mothers)  
  – 53.0 +/-7 yo

• Recipients: 8 MRKH, 1 hyst for cervical ca

• 30 prospective women, extensive evaluation,  
  10 chosen, 1 excluded for bilateral pelvic  
  kidneys. Counseled about national and  
  international options to gain parenthood.
Human UTx – Sweden (n=9)

Vascular anastomoses/surgical technique

• Long vascular pedicles up to and including internal iliac vessels, substantial parts of round ligaments, sacrouterine ligaments, extensive sheet of bladder peritoneum. Preserved uterine branch of UOV (sometimes this branch anastomosed to uterine vein, other times directly to external iliac).

• 2nd team prepped recipient well before anticipated procurement
  – Donor surgery lasted 10-13 hours
  – Recipients 1 and 2 anesthetized 9-10 hours waiting; actual surgery for all recipients lasted 4-5 hours.

• Fixed at round, sacrouterine, lateralized parts of rudimentary uterus (MRKH) or paravaginal connective tissue, extensive bladder peritoneum.
Morbidity

• Donor #2: ureterovaginal fistula (Illb)
• Recipients #1 and #2: POD1-3 pleural fluid (II)
• Recipient #5: blood transfusion for retroperitoneal bleed (II)
Morbidity – hysterectomy (2/9)

• Recipient #2: infection -> hysterectomy
• Recipient #9: thrombosis -> hysterectomy
Human UTx – Sweden (n=9)
Function

• Spontaneous menses within 2 months in 7 pts with regular menstrual patterns
• 10 embryos cryopreserved
• Will start FET 12-18 months after UTx if clinical course uneventful, no rejection for >4-6 months.
• Will remove uterus after 1-2 successful pregnancies
Thank you

- Questions?
- If time...more ethics->
Pakistani context (low-income, pronatalistic countries)

- UFI incidence high
- Strong social pressure to reproduce
- Organ trafficking “rampant”
- Surrogacy and adoption culturally unacceptable
- Difficult to obtain

- Informed consent free of coercion
- Psych eval not easily obtained
- UTn may lead to exploitation of prospective donors and recipients
- Multidisciplinary team unattainable
Pakistani context (low-income, pronatalistic countries)

- Agreement: UTn ethically inadmissable in such contexts.
- Disagreement: should the technology be developed at all?
Ethics continued – what can UTx deliver?

• Sense of ownership ascribed to gestation, even though fetus is created equally from gametes of both parents; likely contributes to motivation
• No nerves included in transplant: absence of sensation in the uterus
• Vaginal delivery not likely feasible: still deprived of vaginal birth experience
• **Transplant patients commonly react with degree of estrangement; uterus is physical and emotional bridge between woman and fetus; feelings of alienation with uterus may compromise feelings with growing fetus**
Ethics continued – what can UTx deliver?

• Criteria currently include that uterus gestated another child
• Physiological rejection can compromise psychological acceptance
• Not a life-sustaining organ; it can be removed. What if removal desired during pregnancy?
• IVF required first; if gestational surrogacy not an option, what is the fate of those embryos? Will pts really be ok with disposal?
Ethics continued – medical harms

- Surgical risks
- Ancillary risks: infection, infarction
- Loss of function
- SE of IS
- Even small risk of rejection in pregnancy risks the fetus; may be increased risk since it is the transplant bearing direct stress of the pregnancy
- Fetus additionally exposed to the above
- ? Premature births vs same rate of prematurity and preeclampsia pre-transplant
- First UTx recipients inevitably human ‘guinea pigs’
Ethics continued – informed consent

- Patients seeking innovative surgery typically focus on perceived benefits
- Response to media reports about UTx: emotive terms “desperate” “unbearable” untempered by discussion of risks
- Early UTx recipients more like “healthy volunteers” than patients who could expect treatment benefit (no live birth so far)
Ethics continued – donor issues

• Emotional pressure on relatives
• Altruistic volunteers less pressure, wouldn’t benefit from closer matching
• Could donor regret giving up chance for parity and be recipient candidate?