Pregnancy in Transplant

UCSF CME- Transplant 2018
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UCSF Division of GI/Hepatology
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Outline:
- Natural history of fertility: end-stage organ disease through transplant
- Contraceptive recommendations
- Pregnancy effects on maternal, fetal and graft health
- Breastfeeding

Infertility In End-Stage Organ Disease

- **End-Stage Liver Disease (ESLD):**
  - ~75% of pre-menopausal women listed for LT have secondary amenorrhea

- **End-Stage Renal Disease (ESRD):**
  - Most (> 90%) women on dialysis have oligo/amenorrhea
  - Among women with ESRD with regular menses, 50% ovulatory

Disclosures

- None
Impaired Hypothalamic-Pituitary-Ovarian Axis

- Pulsatile release of GnRH & LH is impaired
- FSH= Follicle development, estradiol production
- LH surge= Important for release of egg

Sex Hormone Levels Normalize After Transplant

Most (~75%) transplant patients have regular cycles within one year of transplant…menses may resume within weeks

Reproductive Health Counseling

- >30-40% of female solid organ transplant recipients are child-bearing age
- Family planning may not come to mind
- With careful planning- most recipients have successful pregnancies
- Unplanned pregnancies can increase risks to moms, grafts, and babies

Contraception Use After Transplant

- European study, assessed contraception use in KT & LT pts
- Survey conducted at mean 5 yrs post transplant

<table>
<thead>
<tr>
<th>Post-transplant Group (n = 67)</th>
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<tbody>
<tr>
<td>No contraception</td>
<td>48.3%</td>
</tr>
<tr>
<td>Oral contraception</td>
<td>5.7%</td>
</tr>
<tr>
<td>Contraceptive patches</td>
<td>2.3%</td>
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<tr>
<td>Intrauterine device</td>
<td>3.4%</td>
</tr>
<tr>
<td>Condoms</td>
<td>34.3%</td>
</tr>
<tr>
<td>Natural methods</td>
<td>2.3%</td>
</tr>
<tr>
<td>Cusus interruptus</td>
<td>5.7%</td>
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</table>

33% of pregnancies in transplanted women were unplanned
Contraceptive Knowledge and Practice in the U.S.

- n=183 transplanted women, 19-49yrs
- ~60% of women never received contraception counseling in pre/post-transplant setting
- >50% not using contraception at time of survey
- 44% not aware that pregnancy possible after transplant

French et al, Obstet Gynecol 2013

Contraceptive Options

- Intrauterine Device (IUD)
  - Levonorgestrel (LNG)
  - Copper

Intrauterine Device (IUD)

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- Copper

- Skyla & Mirena
  - Low dose of progesterone
  - Lessened menstrual bleeding
  - Thicker cervical mucus
  - Can prevent ovulation

- ParaGard
  - Copper
  - Increases cervical mucus
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Intrauterine Device (IUD)

Copper

Historical concerns:
- Lower efficacy of IUD with IMS\(^1\)
  - Transplant IMS acts primarily on T cells, with preserved macrophage activity\(^2\)
- Risk of pelvic inflammatory disease (PID)
  - No increased PID risk in either general or immuno-compromised populations\(^3\)\(^-\)\(^5\)


IUD Efficacy Post Transplant

- n=647 Chinese women post KT
- 15.5% had unwanted pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Follow-up</th>
<th>Transplant</th>
<th>IUD</th>
<th>Pregnancy</th>
<th>PID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juliato 2018</td>
<td>25</td>
<td>Median 6.3 yrs</td>
<td>KT, LT</td>
<td>LNG</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Huguelet 2017</td>
<td>6</td>
<td>18-32 months</td>
<td>KT, LT</td>
<td>LNG</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ramhendar &amp; Byrne 2011</td>
<td>11</td>
<td>38 months</td>
<td>KT</td>
<td>LNG</td>
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<td>Xu 2011</td>
<td>178</td>
<td>≥ 6 mo</td>
<td>KT</td>
<td>-</td>
<td>0</td>
<td>*</td>
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<tr>
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<td>1</td>
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<td>KT</td>
<td>LNG</td>
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<tr>
<td>Zemer 1981</td>
<td>2</td>
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<td>KT</td>
<td>Copper</td>
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- Failure rates: copper 0.8% and LNG 0.2%

* Not reported

Xu et al, Eur J Contraception Reprod Health Care 2011
Combined Hormonal Contraceptives (CHC)

- Estrogen + progestin; 9% failure rate
- Safety concerns- VTE (1/1,000), cholestatic liver injury, stroke, HTN, P450 interactions- no controlled studies in transplant patients
- KT: n=26 pill & n=10 patch users followed 18-36 mo:
  - 1 thrombophlebitis and 1 graft failure (10 yrs post KT) with pills; ~ 35% users required increased BP meds
- LT: n=10 pill & n=6 patch users followed 12 months
  - 1 pt on high dose pills developed cholestasis

Progestin-Only Methods

- Progestin only pill (POP):
  - No increased risk of clots of high BP\(^1,2\)
  - Failure rate 9%; take at same time EVERY day
- DMPA (Depo-Provera):
  - Injected every 12 weeks, failure rate 6\(^3\)
  - 2004 FDA warns of bone loss, though resolves with cessation of use\(^4\)
  - Greater risk of impaired bone health in transplant women
- Implant (ie Nexplanon): Not studied in transplant
  - Less effect on bone health\(^5\); failure rate 0.05\(^3\)

CDC Recommendations: Contraception After Solid Organ Transplant

<table>
<thead>
<tr>
<th>Graft Condition</th>
<th>Copper IUD</th>
<th>Hormonal IUD</th>
<th>CHC (pill, patch, ring)</th>
<th>POP</th>
<th>DMPA</th>
<th>Implant</th>
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<tr>
<td>Uncomplicated</td>
<td>1</td>
<td>2</td>
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Complicated = acute or chronic graft failure, rejection, or cardiac allograft vasculopathy

Adapted from WHO Medical Eligibility Criteria for Contraceptive Use; Centers for Disease Control, MMWR Recomm Rep 2016.
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1 = No restriction  
2 = Benefits outweigh theoretical or proven risks  
3 = Risks may outweigh benefits  
4 = Unacceptable risk

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### CDC Recommendations: Continued Contraceptive With Graft Complications

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What Does “Complicated” Graft Function Really Mean?

- Complicated = “acute or chronic graft failure, rejection, or cardiac allograft vasculopathy”
- Impaired liver and kidney function primarily affects safety of estrogen containing agents (ie CHC)

**Reasonable thresholds for CHC use¹:**
- GFR >/= 90, no proteinuria
- Controlled blood pressure, BP < 130/90 mmHg
- No liver decompensation (ascites, encephalopathy, variceal bleeding)²

¹Sarkar et al, Am J Transplant 2018; ²Kapp et al, Contraception 2009

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**Pregnancy After Transplant: Timing**

- AST Consensus Statement (2005): Safe to pursue at 1 year
- minimal immunosuppression
- lower risk of infectious complications
- allows sufficient time for stable graft function

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**Maternal and Fetal Risks**

- MOM
  - Rejection
  - Diabetes
  - HTN
- BABY
  - Spontaneous abortion
  - Birth defects
  - Growth restriction
  - Pre-term delivery (< 37 weeks)

McKay et al, Am J Transplant 2005
### Maternal and Fetal Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Kidney (n=4768)</th>
<th>Liver (n=450)</th>
<th>Non Transplant (n=4060)</th>
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<tr>
<td><strong>HTN</strong></td>
<td>54.2%</td>
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<tr>
<td><strong>Birth weight</strong></td>
<td>2420g (5.3lbs)</td>
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Graft Outcomes: National Transplant Pregnancy Registry

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Kidney Transplant (n=1005)*</th>
<th>Liver Transplant (n=238)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rejection during pregnancy</td>
<td>0.8%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Post-partum rejection</td>
<td>1.8%</td>
<td>4.4%</td>
</tr>
</tbody>
</table>

Overall risk of rejection is low; Not clear whether rejection in pregnancy associated with graft loss

*Primary IMS: 26% AZA/pred, 47% CSA, 27% Tac
**Primary IMS: 42% CSA, 55% Tac

Pregnancy After Transplant

> 75% of liver and kidney transplant recipients have successful deliveries

Deshpande et al, Am J Transplant 2011; Deshpande et al, Liver Transplant 2012; Blume et al, Best Practice & Research Clinical Obstetrics and Gynecology 2014

Pregnancy After Transplant: Health of Baby

What are risks of IMS to infants?
### Immunosuppression in Pregnancy

<table>
<thead>
<tr>
<th>IMS</th>
<th>FDA Safety Class</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>B- No evidence of risk in humans</td>
<td>Controversial risk of cleft palate, larger studies failed to show consistent increased risk.</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>C- Risks cannot be ruled out</td>
<td>- May be associated with pre-term birth and low birth weight, transient fetal renal insufficiency/hyperkalemia. - Incidence of birth defects no different than general population.</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>C- Risks cannot be ruled out</td>
<td>- Incidence of birth defects no different than general population.</td>
</tr>
<tr>
<td>Sirolimus/everolimus</td>
<td>C- Risks cannot be ruled out</td>
<td>Limited data on mTOR inhibitors in pregnant patients. Given anti-proliferative effects NOT recommended in pregnancy.</td>
</tr>
<tr>
<td>AZA</td>
<td>D-Positive evidence of risk</td>
<td>Associated with prematurity and low birth weight. Neonatal leukopenia, low plt, low immunoglobulins resolve by 1 year.</td>
</tr>
<tr>
<td>MMF</td>
<td>D-Positive evidence of risk</td>
<td>Contraindicated in pregnancy- associated with miscarriage, and facial malformations affecting ears, limbs, heart, esophagus, and kidney.</td>
</tr>
</tbody>
</table>

Azathioprine

- Category D due to animal studies noting teratogenic effects
- Human data have not supported these observations
- Sporadic cases of congenital malformations in humans not greater than general population
- Uncommon immunodeficiency (leukopenia, low plt, low immunoglobulin levels) - resolve by 1 year

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<td>AZA</td>
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<td>MMF</td>
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</table>

Mycophenolic Acid Products (ie cellcept, myfortic)

High risk of birth defects (22% incidence)1-2
- Ears, oral-facial, limbs, heart, esophagus, kidney
- Pregnancy test before and during therapy
- Report pregnancy exposures to Mycophenolate REMS (Risk Evaluation and Mitigation Strategy) program / Transplant Pregnancy Registry (TPR)

Two methods advised if failure rate >1%
(IUDs sufficient as single agent)3

Breast Feeding After Transplant

**Breast Feeding After Transplant**

National Transplantation Pregnancy Registry (NTPR) Data

- Contantinescu et al, Best Practice & Research Clinical Obstetrics and Gynecology 2014

**Tacrolimus and Breastfeeding**

- Tacrolimus levels in blood and breast milk
  - Infant exposure through breast milk <0.3% of mother's weight-adjusted dose
  - Among 15 infants, 11 exclusively breastfed
  - No difference in tacrolimus levels between breastfed and formula fed infants


**Cyclosporine and Breastfeeding**

- With therapeutic CSA levels, amount in breastmilk <1%–2% of maternal levels
- No reported adverse effects on infant growth or kidney function

Morelli et al, Transplantation 2002; Maroco-Ferreira et al, Obstet Gynecol 2001;
Hjorthøj et al, Transplantation 1998; toxnet.nlm.nih.gov

**Azathioprine and Breastfeeding**

- Doses up to 200mg per day: low to unmeasurable active metabolite in breastmilk or infant blood
- No reported adverse effects on immunity, infection or growth in kids followed up to 3.5 years (longer follow-up lacking)

3. Angstbauer et al, J Crohns Colitis 2011
Breast Feeding After Transplant: Safe?

<table>
<thead>
<tr>
<th>Medication</th>
<th>Safe per LACTMED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Probably safe per LACTMED- minimal exposure to infant</td>
</tr>
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<td>Sirolimus/everolimus</td>
<td>No human data. Avoid</td>
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<td>Azathioprine</td>
<td>Probably safe per LACTMED- minimal exposure to infant</td>
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<tr>
<td>Mycophenolic acid</td>
<td>No human data for nursing. Teratogenic in pregnancy. Avoid</td>
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Summary

- Impaired fertility is common in end-organ disease
- Transplant usually restores fertility
- Discuss family planning throughout the course of pre and post transplant care
- IUDs: low failure rate, minimal/no drug-drug interactions, favorable safety profile

Learn More!

- International Transplant Nurses Society (www.itns.org)
  - Sexual Health After Transplant
  - Pregnancy and Parenthood After Transplant
- American Society of Transplantation (myast.org)
  - Parenthood After Transplantation
- TransplantPregnancyRegistry.org