Post-transplant Pregnancies: The Promises and Perils

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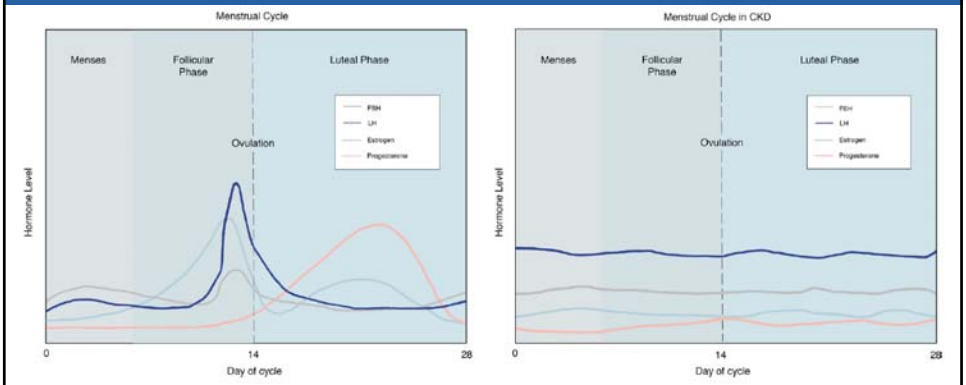
Learning objectives

- Special considerations for pregnancies post-transplantation
  - Immunosuppressive medications
- Maternal and offspring outcomes in kidney and kidney-pancreas transplant recipients
- Optimizing outcomes of pregnancies after transplantation

Fertility and Kidney Disease

Reduced Fertility in Chronic kidney disease (CKD)

- Fertility is 1/100th of the general population
- Disruption of Hypothalamic-pituitary-ovarian axis
  - Anovulatory cycles and amenorrhea



Dumanski, J of Neph, 2019

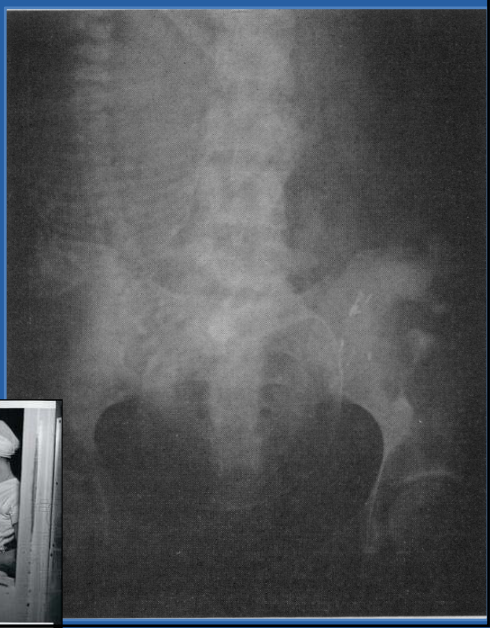
Fertility improves after transplant

- ~ 70% regular menses
- ~ 45-70% ovulatory cycles
- Pregnancy is possible as fertility improves
  - 44% unaware of the possibility of pregnancy
  - Fertility is 1/10th of general population
- Fertility goals are important for quality of life

Pietrzak, Transplant Proceeding, 2006
French, Obstet Gynecol, 2013
Matas, Clinical Transplantation, 2002

Historical Perspective

- First successful kidney transplant in a female- 11/1956
- Conceived – 7/1957
- Cesarean section
- Healthy infant



Murray, NEJM 1963
Murray, AJT 2011

SOT recipients and pregnancy

First Reported Pregnancies in Solid Organ Transplant Recipients		
Organ	**Year**	**Special Comments**
Kidney		
Identical twin donor	1957	Within 1 yr of transplant
Non-twin donor	1966	Within 1 yr of transplant Vaginal delivery
Liver	1978	Infertility prior to transplant
Pancreas (simultaneous kidney pancreas)	1986	
Heart	1988	
Lung	1996	
Intestine (prior liver transplant)	2006	

New challenges after transplant

- Is pregnancy safe for me?

- Is there a risk to my transplant?

- What are the risks to my child?

Adapted from Rao ; Med Clin N Am, 2016

Transplant Pregnancy Registry International

Transplant Pregnancy Registry International
A DIVISION OF GIFT OF LIFE INSTITUTE

- Previously National Transplantation Pregnancy Registry (NTPR)
- Established in 1991
- 27th year of continuous data collection
- Voluntary registry

TPR: Female recipients and pregnancies

Organ	Recipients	Pregnancies	Outcomes
Kidney	1,101	1,980	2,062
Liver	281	575	579
Kidney-Pancreas	63	114	120
Heart	92	160	165
Lung	33	44	46
Other	29	39	45
Totals	1,599	2,912	3,017

TPR Annual Report 2017

Post-transplant Pregnancies: Immunosuppressive Medications

Pregnancy consideration for immunosuppressive medication

- Teratogenic risk?
  - Specific pattern for malformation
- Metabolism changes and dose adjustment?
- Breast feeding?
- Long term effects on the immune system of the child?

FDA categories for safety in pregnancy

FDA category	Comments
A	No risk
B	No risk in animal studies, but there is not sufficient data in human
C	Animal studies have shown risk, but human risk not established
D	Human risks well established, evaluate risk-benefit ratio
X	Definite risks, risks outweighs benefits in most cases

Immunosuppressive medication and FDA category

Medication	FDA category
Mycophenolic Acid (MPA) Mycophenolate mofetil Mycophenolate sodium	D
Azathioprine	D
Prednisone	C
Calcineurin inhibitors (CNI) Cyclosporine Tacrolimus	C
Mammalian target of Rapamycin Sirolimus Everolimus	C
Belatacept	C

Adapted from Rao, Med Clin N Am (2016) 613-629

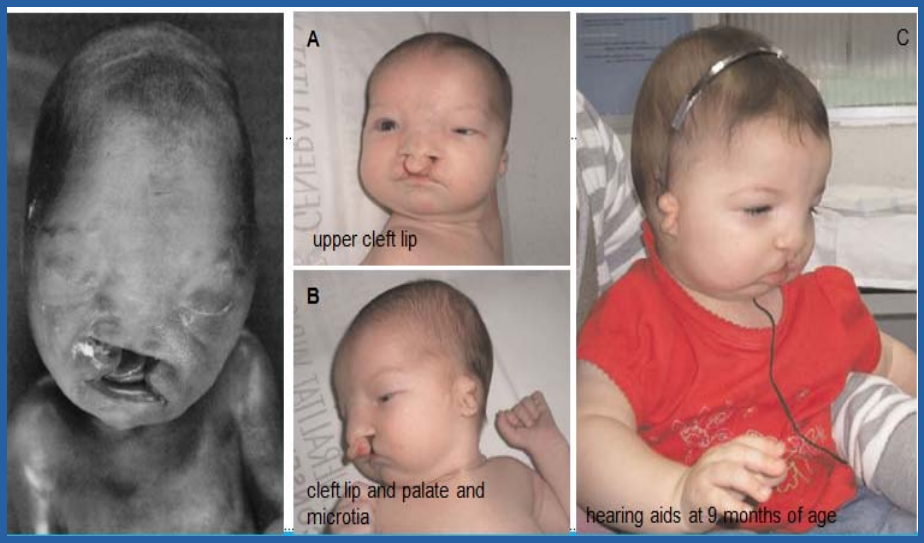
Mycophenolic acid (MPA)

FDA category
D

- Mycophenolate mofetil & Mycophenolate sodium
- Up till 2007, MPA agents were FDA category C
- Concerning pattern with MPA was noted by TPR
- High rate of miscarriage (50%)
- In live birth
  - High rate of birth defects (25%)
  - Mycophenolate embryopathy

Sifontis NM,Transplantation,2006

Mycophenolate embryopathy



Mycophenolic acid (MPA)

FDA category
D

- Advise to use effective contraception
- Discontinue 6 weeks prior to conception
- Secreted in breast milk (animal studies)
- Breast feeding not recommended

Sifontis NM,Transplantation,2006
Constantinescu S, Best Practice& Clinical research, OBGYN 2014

Azathioprine

FDA category
D

- Despite the FDA category, **safe** in pregnancy
- Animal studies with high doses (5mg/kg/d) had fetal malformation
- Usual dose in transplant: 0.5 to 1.5mg/d
- Acceptable substitute for MPA
- No dose adjustment needed during pregnancy
- Transient immune alteration in neonates
- Low level in breast milk (<1% maternal dose)
- Breast feeding is acceptable

Rao, Med Clin N Am, 2016
Constantinescu S, Best Practice& Clinical research, OBGYN 2014

Prednisone

FDA category
C

- Fetal malformation rate 3.5%
  - Similar to general population
- No specific pattern of malformation
  - Cleft lip?
- No dose adjustment needed during pregnancy
- Rare neonatal defects at high doses
  - cataract, adrenal insufficiency and infection.
- Very low level in breast milk
- Breast feeding is acceptable

Rao, Med Clin N Am, 2016
Constantinescu S, Best Practice& Clinical research, OBGYN 2014

Calcineurin inhibitors

FDA category
C

- Cyclosporine & Tacrolimus
- Fetal malformation rate 3.5-5%
  - Similar to general population
- No specific pattern of birth defects in humans
- Dose adjustments
  - Dose increase of 20-25% during pregnancy
  - Rapid decrease in dose immediately after delivery
- No significant effects noted in neonate
- Breast feeding is acceptable

Rao, Med Clin N Am, 2016
Kim, Clin transplant, 2015
Fisher, Am J transplant, 2005
Constantinescu S, Best Practice& Clinical research, OBGYN 2014

Other medications

FDA category
C

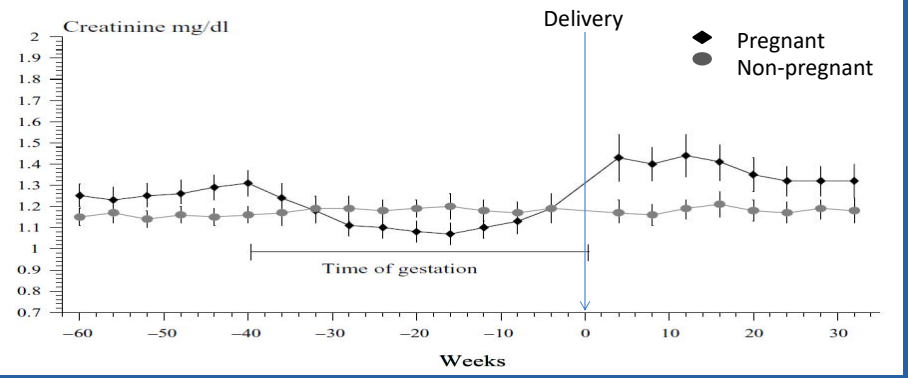
- **Mammalian target of Rapamycin**
  - Sirolimus – Limited data
  - Everolimus – Very limited data
- Belatacept
  - Very limited data

Rao, Med Clin N Am, 2016
TPR, Annual report 2017

Post-transplant Pregnancies: Physiological Changes in Allograft

Physiological changes in pregnancy

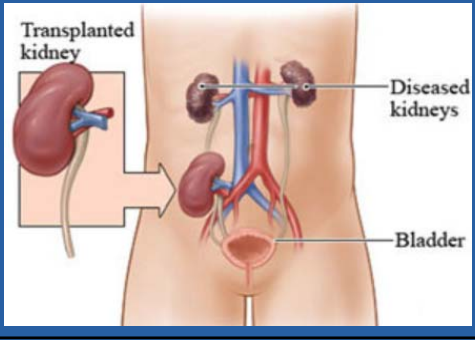
Kidney	Kidney Allograft
- 50% increase in plasma volume - 40-65% increase in renal plasma flow - 50% increase in GFR	Solitary kidney - Can it meet the increase in demand?

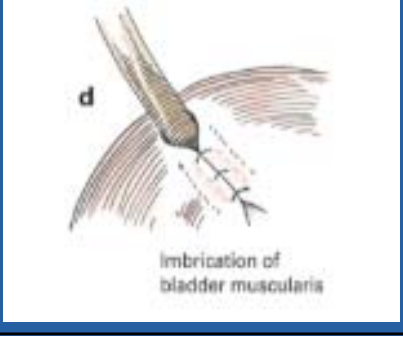


Fisher. Am J transplant. 2005

Physiological changes in pregnancy

Kidney	Kidney Allograft
Normal creatinine 0.4-0.8mg/dl	Depends on baseline creatinine
Proteinuria of up to 300mg/d	Depends on baseline proteinuria
Urinary stasis - Hormonal changes - Pressure from the gravid uterus - Physiological hydronephrosis (Rt>Lt)	**Very prone to UTI (40%)**





Physiological changes in pregnancy

Cardiac	Heart Allograft
Increase in cardiac output to 40% - Increase in stroke volume - Increase in heart rate Uterine contractions during labor leads to 300-500cc of auto-transfusion	Physiological changes are generally well tolerated Echo and RHC show stable function - Decrease should promote evaluation. Increase predisposition to arrhythmia
Respiratory	**Lung Allograft**
- 40-50% increase in minute ventilation due to increase in tidal volume - FVC decreases - FEV1 stable	Physiological changes are generally well tolerated FEV1 remains stable - Decrease in FEV1 should promote evaluation

Physiological changes in pregnancy

Glucose Metabolism	Pancreas Transplant
Diabetogenic state - Insulin resistance in mother and increase glucose transfer to the fetus. - Beta-cells hyperplasia and increase insulin secretion	Physiological changes are generally well tolerated New insulin requirement needs evaluation for graft dysfunction
Liver	**Liver Allograft**
Metabolic demands Cholestasis state	Physiological changes are generally well tolerated Normal transaminase level

Outcomes:
Maternal, Graft, and Offspring

Pre-conception: High risk maternal characteristics

- Pre-conception HTN
  - 40-44%
    - Vs 5% in US general population
- Pre-conception DM
  - 5-14%
    - Vs 0.9% in US general population

TRP-I, Annual rpt 2016
Wyld,AJT, 2013
Gill, AJT, 2009
ACOG, HTN in pregnancy, 2013
Martin, Birth 2017, Natl Vital Stat Rep

Maternal characteristics

	Kidney	Liver	Kidney-Pancreas	Heart	Lung
Recipients	**1100**	**281**	**63**	**92**	**33**
Pregnancies	**1980**	**575**	**114**	**160**	**44**
Age at 1st transplant (yrs)	**24 ± 6**	**21 ± 9**	**30 ± 3**	**20 ± 9**	**27 ± 6**
Txp-to-conception interval (yrs)	**5.3 ± 4**	**7.3 ± 6.2**	**4.3 ± 3**	**7.5 ± 5.9**	**3.9 ± 3**
Pre-transplant pregnancy	**28%**	**25%**	**39%**	**27%**	**49%**
Unplanned pregnancies	**32%**	**47%**	**35%**	**38%**	**61%**

TPR, Annual report 2017

Maternal and graft outcomes

	Kidney	Liver	Kidney-Pancreas	Heart	Lung
During pregnancy					
Hypertension	48%	22%	57%	46%	52%
Diabetes	8%	8%	3.5%	9%	34%
Pre-eclampsia	31%	24%	42%	27%	15%
Rejection	1%	4.5%	5%	9%	16%
After pregnancy					
Postpartum rejection	1.3%	5%	4.4%	7%	14%
Graft loss within 2 yrs of delivery	5.6%	4%	11%	2%	7%

- Pregnancy in general US population-

HTN 10%, DM 5%, Pre-eclampsia 5% (w/o HTN) 15-40% (w/ hx of HTN),

TPR, Annual report 2017

Kidney transplant recipients: Pregnancy does not impact graft survival

Davidson et al AJKD 1995

18 pregnant and 18 matched control

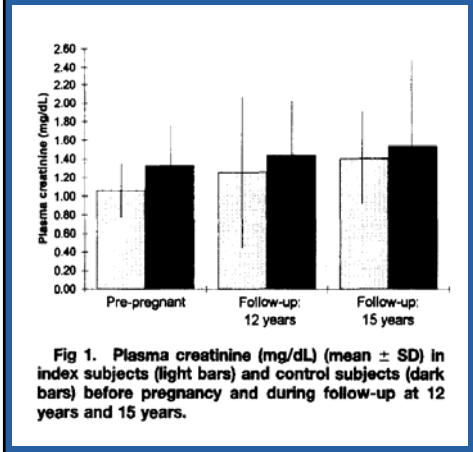
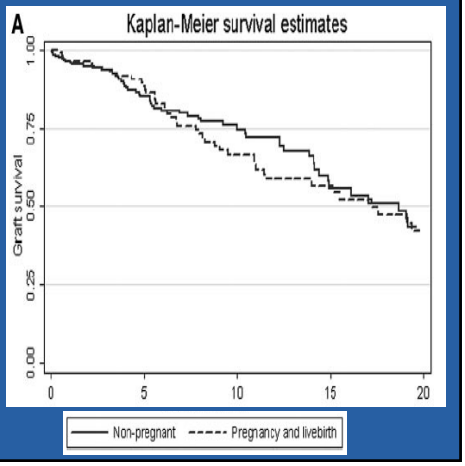


Fig 1. Plasma creatinine (mg/dL) (mean ± SD) in index subjects (light bars) and control subjects (dark bars) before pregnancy and during follow-up at 12 years and 15 years.

Levidiotis et al JASN 2009

120 pregnant and 120 matched control



Kidney transplant recipients: Pregnancy does not impact patient survival

Fischer et al AJT 2005

81 pregnant and 81 matched control

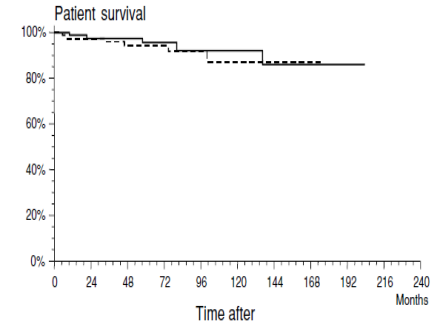
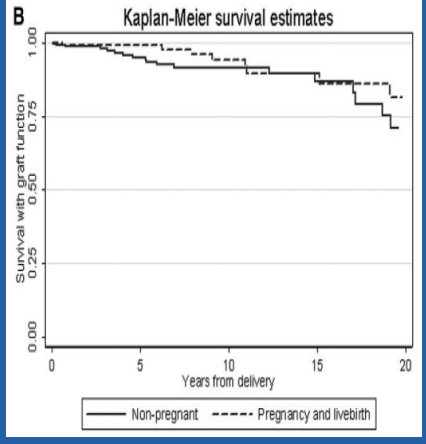


Figure 1: Postpartum patient survival in study subjects (solid line) and controls (dashed line; n.s.).

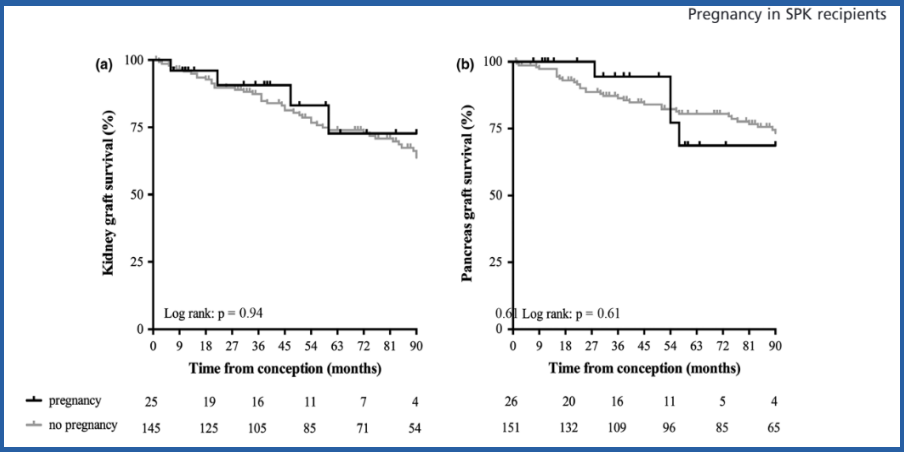
Levidiotis et al JASN 2009

120 pregnant and 120 matched control



Kidney pancreas transplant recipients:

Pregnancy does not impact long term graft survival



Normand, Txp Int, 2017

Pregnancy outcomes

	Kidney	Liver	Kidney-Pancreas	Heart	Lung
Pregnancy Outcomes	2062	579	120	165	46
Live Births	75%	69%	69%	67%	59%
Gestational age	36 ± 3	37 ± 3	34 ± 3	36 ± 3	34 ± 5
Prematurity (<37 weeks)	51%	39%	76%	41%	56%
Birth weight	2571 g (5.7 lbs)	2739 g (6.0 lbs)	2135 g (4.6 lbs)	2600 g (5.7 lbs)	2185 g (4.8 lbs)
Low birth weight (<2500 g)	41%	30%	63%	37%	59%
Cesarean section	52%	43%	69%	42%	41%
Neonatal deaths	1.4%	1%	1%	0	11%

TPR, Annual report 2017

Long-term offspring outcome

- Pre-term with all its implications
- Catch up growth within 1 yr of birth
- Excellent long term neurological development
  - No increase in development delays
  - IQ scores- within expected range
- Concern for altered T-cell population may affect vaccination and long-term immunity
- Average age of offspring at maternal death
  - 4 yrs in children of lung transplant recipient
  - 16 yrs in children of kidney transplant recipient

TPR, Annual rpt ,2017

Stanley, Transp Proc, 1999

Pregnancies Post-transplant: Optimizing Outcomes

General principles

- Overall good maternal health
- Stable and adequate graft function
- Stable and appropriate immunosuppressive medication regimen
- No acute infections that can impact the fetus
- Optimal transplant to conception interval

Adequate graft function

- Kidney
  - Creatinine < 1.5mg/dl
  - Minimal to no proteinuria (<500mg/d)
- Limited data in other organs
  - High prevalence of CKD in transplant recipients

Pre-conception kidney graft dysfunction portends poor outcomes

	Serum creatinine before pregnancy		
	<1.4mg/dl	1.4-1.8mg/dl	>1.8mg/dl
Preeclampsia	24	45	60
Preterm delivery	35	70	90
Loss of >25% renal function post-partum	4%	7%	35%

Armenti , High risk pregnancy: Management option, Elsiver 2011

Ideal transplant to conception interval

- Waiting period of 1-2 year prior to conception
  - Recovery from transplant surgery
  - Time to achieve stable graft function
  - Transition to non-MPA based immunosuppressive regimen
  - Decreased risk of infections eg. CMV

McKay and Josephson, AJT 2005

Greater success with longer TCI

Transplant to conception interval	Non-viable Outcomes
Less than 6 months	47%
6-24 months	27.6%
More than 24 months	19.4%

- 53% of pregnancies within 6 months of transplant result in viable birth
- Individualize plans for pregnancies that occur during the 1st year of transplant

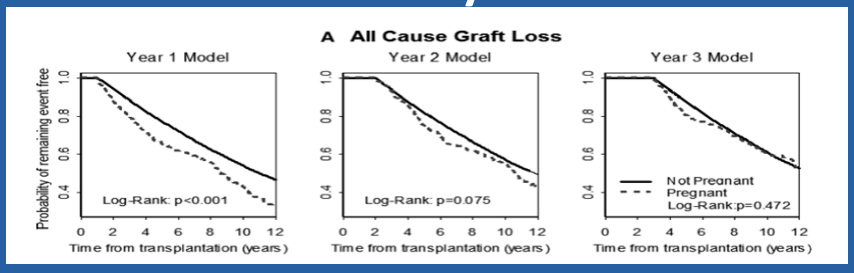
Constantinescu, ATC 2011

Successful pregnancies are possible even in >10yr post-transplant

Transplant to conception interval	Live Birth
2 to < 5yrs	85%
5 to < 10 yrs	83%
>10 yrs	88%

Constantinescu, ATC 2015

Better kidney graft outcomes with >2yr TCI



Rose, Am J Transplant, 2016

Causes of graft loss different

Table 4: Cause of allograft failure among women who did or did not become pregnant in the first 3 posttransplant years (percentages shown)

	Women who become pregnant in the first 3 posttransplant years N = 424/729 (58%) allograft failures[1]	Women who did not become pregnant in the first 3 posttransplant years N = 10 638/21 085 (50%) allograft failures
Death with function	40 (12.5)	22 385 (29.5)
Acute rejection	50 (15.5)	841 (10.4)
Chronic rejection	165 (51.1)	3347 (41.4)
Recurrent disease	14 (4.1)	307 (3.8)
Infection	2 (0.6)	65 (0.8)
Other	52 (16.2)	1140 (14.1)

Rose, Am J Transplant, 2016

Achieving optimal timing of pregnancy: CONTRACEPTION

- Key to pregnancy and graft outcomes.
- Unacceptable high rate of unplanned pregnancies (30-60%).
- Decrease rate of MPA exposure.
- Optimize pre-conception factors
- Transplant care providers need to take an active role in contraception education.

Contraception

	Pregnancy rate		Benefits	Problems
	Correct use	**Typical use**		
Intrauterine devices			Effective Long acting	
- Copper	<1%	<1%		Heavy menses
- Progesterone	<1%	<1%		Irregular bleeding
Progesterone implant	<1%	<1%	Effective Long acting Decrease anemia	
DPMA injection	<1%	6%		Decrease BMD
Contraceptive pills	<1%	9%		Many- HTN, VTE
Condom (male/female)	2-5%	18-20%	STI prevention	

Pregnancies Post-transplant: Practical Approach

Transplant Provider Role

- Provide a safe environment
- Bring up the topic of sexuality and reproductive health
- Keep an open mind
- Respect patient autonomy
- DO NOT take a paternalistic approach
- Provide guidance and advice

Pre-transplant

- Discuss fertility goals
  - Ask about hope and aspirations
  - Discuss general principles of successful outcomes
  - Educate about maternal, graft, and offspring outcomes
  - Evaluate for inheritable diseases
  - Discuss and ADVICE on contraception
    - Progesterone implant or IUDs
- Vaccination
  - Check immune status for common infection.
  - Give live vaccines (eg. MMR) which cannot be given post-transplant

Rao, Med Clin N Am, 2016

Post-transplant

- Continue dialogue about fertility goals
- Make contraception discussion a priority

Pre-conception

- 1-2 years after transplant
- No rejection episode in last 1 year
- Optimize graft function
- Optimize management of co-morbidities
  - HTN
  - DM
  - Smoking cessation

Rao, Med Clin N Am, 2016

Pre-conception (continued)

- Infection risk profile
  - Vaccinations
- Stop MPA for at least 6 wk
- Review and stop other medications with high fetal risk
  - ACEi/ARB
  - Statins
- Start prenatal vitamin and folate supplement
- Consider aspirin for prevention of pre-eclampsia

- Once optimized, then stop contraceptive

Rao, Med Clin N Am, 2016

Prenatal

- Early diagnosis and referral to high-risk obstetrics care
- Serial monitoring of graft function
  - Biopsy for unexplained graft dysfunction
- Serial monitoring of immunosuppressive medication
  - Dose adjustment for calcineurin inhibitor
  - Morning sickness and hyperemesis gravidum

Rao, Med Clin N Am, 2016

Prenatal (continued)

- Optimize blood pressure and glycemic control
- Monitor for preeclampsia
- Monthly urine culture
- Nutrition
  - Calcium and vitamin D
- Anemia
  - IV iron
  - Erythropoietin stimulating agents

Rao, Med Clin N Am, 2016

Fetal monitoring

- High risk of intra-uterine growth restriction
  - Serial ultrasounds
- High risk for pre-term
- Steroids for lung maturation

Delivery

- Monitor hemodynamics carefully
- Vaginal delivery preferred
- Caesarean section for obstetrics indication only
  - >50% caesarean section in transplant recipients vs 30% in general population.
  - Multitude of underlying reasons
    - high risk pregnancies
    - fetal distress
    - provider and patient preference

Rao, Med Clin N Am, 2016

Caesarian section

- Epidural anesthesia preferred
- Careful not to injure the pelvic allograft organs
  - Transplant ureter
  - Transplant pancreas
- Cardiac transplant recipients
  - Intensive monitoring is needed in special cases
- Lung transplant recipients
  - Precaution during intubation
  - Impaired cough reflex
    - Bronchial hygiene post-surgery

Post-partum

- Clinical and laboratory monitoring for graft function
  - Graft dysfunction may require biopsy
- Immunosuppression
  - Dose adjustment of calcineurin inhibitor
  - Review immunosuppressive medication
- Do not use NSAIDs for pain control
- Breast feeding counselling
- Contraception counseling

Summary

Summary

- Fertility improves after transplantation.
- Use contraception to wait 1-2 years after transplant to convince.
- Optimize graft function and comorbidities prior to conception.
- Stop MPA at least 6 weeks prior to conception.
- A well functioning allografts respond well to the increase physiological demands of pregnancy.

Summary

- Pregnancies post transplant have high live birth rate, but usually deliver 1 month early, mostly by cesarean section, and have high rates of low birth weight.
- No increase birth defect (unless MPA exposure).
- These are high risk pregnancies requiring multidisciplinary care.
- Long term patient, graft and offspring outcomes needs further monitoring.

Summary:
Pregnancy after transplant is a success story*

* In selected patients

Acknowledgement

- Dr Constantinescu, MD PhD
- Transplant Pregnancy Registry International – staff and patients
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- Outside of US: 01-215-599-2078