Anesthetic management of pregnant patient after solid organ transplantation

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Dr. Joseph Murray

When Nobel laureate winner, Joseph E. Murray, MD, and his colleagues transplanted a kidney from Ronald Herrick into his identical twin, Richard, on December 23, 1954, it was the first time an organ from one individual had ever been successfully transplanted into another.

It is estimated that as of June 2013, there were

~ 200,000 recipients alive with a functioning kidney transplant
~ 65,000 recipients alive with a functioning liver transplant.
25% of these recipients are women of reproductive age





Organ Donati	on and Transplantation Activities						
2014		World Health Organization	(Global A		organ Transpl Estimates	antation
Sont World Health		Kidney	Liver	Heart	Lung	Pancreas	Small bowel
ORGANIZACIÓN NACIONAL DE TRASPLANTES			26151	6542	4689	2328	215
Last data available: April, 2016		≈ 1 ≤ 1 41. trai	.81 % of inc 0% of globa 6% of living nsplants	kidney tra	2013 Insplants and		





- 21 y old patient from Oklahoma
- One of a pair of identical twin females
- With a three year history of chronic glomerulonephritis
 - Uncontrolled HTN 190/120 mmHg
 - CHF
 - Severe oral and gastrointestinal hemorrhage
 - Extra-corporeal hemodialysis
- Successful renal transplantation
- Publication in 1963



- The first pregnancy after
 - kidney transplantation occurred in 1958
 - and after liver transplantation in 1977
- The National Transplantation Pregnancy Registry (NTPR) began collecting data from recipients in North America in 1991.

	splantation Pregnancy Registered From January 014
A 11 1 A	

Solid Organ(s) Transplanted	Recipients	Pregnancles ^c	Live Births
Kidney	986	1742	1333 ^d
Liver	233	431	310 ^e
Liver-kidney	8	11	12
Kidney-pancreas	58	104	77 ^r
Heart	78	133	91 ^g
Heart-lung	5	5	5
Lung	28	37	22
Total	1396	2463	1850

Anesthetic approach to parturient after solid organ transplantation

Question number 1: Timing of pregnancy after transplantation

- Gonadal dysfunction resolved ~ 6 month after renal transplantation
 Am J Transplant 2005;5:1592–9
- Limited data for heart, lung and heart-lung transplantation

• The **2005** American Society of Transplantation Consensus conference suggested that: *Pregnancy 1 year after transplant is safe as long as the patient has stable graft (renal) function*

Timing of pregnancy after transplantation Graft function

Table 2. Graft Function Assessment of Transplanted Organs During Pregnancy

Kidney GFR, creatinine, proteinuria. ³ Creatinine < 1.5 mg/dL and minimal or no proteinuria are defined as indicators of a well-functioning renal allograft. ⁴ F Liver If liver enzymes (AST, ALT, alkaline transferase) or function tests (bilirubin, INR) are elevated 1.5 times or more than the upper limit of normal, further evaluation is recommended to exclude liver allograft dysfunction. ⁶ If Heart ECG, echocardiogram, CXR, cardiac catheterization. ⁹ If For evaluation of rejection, the "gold standard" is endomyocardial biopsy, done when there is a clinical suspicion of rejection. ^{9,10} If Chronic allograft rejection usually presents as accelerated coronary artery disease. Patients may present with severe dysrhythmias, CHF, and silent MI on ECG. ^{11,12}	Transplanted		
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		gradient increases. ¹⁴	

regnancy changes in kidney function, as well as hypertensive disorders of pregnancy, can confound or mask alterations in graft function.⁵ Signs and symptoms of preeclampsia such as headache, blurry vision, right upper quadrant pain, elevated LFTs, and thrombocytopenia differentiate preeclampsia from graft dysfunction.

Considerations During Pregnancy

- During normal pregnancy, alkaline phosphatase levels increase and serum transaminases increase to the upper limit of normal⁷; however, bilirubin level and prothrombin time do not change.⁸ Therefore, baseline liver function results obtained before pregnancy allow for more accurate interpretation of changing levels during pregnancy.
- At a minimum, a baseline ECG and echocardiogram should be performed.

t generally is accepted that rejection rate is not increased in pregnant heart transplant recipients.¹⁰ Patients however, who had a heart transplant secondary to PPCM appear to be at an increased risk of rejection within the first year after transplant compared with other heart transplant patients and a theoretical risk of recurrent PPCM.¹⁰

Data are lacking regarding adaption of the transplanted lung to pregnancy. Based on a limited case series, the risk of rejection, graft loss, and mortality among lung transplant recipients who become pregnant may be higher compared with other solid organ transplants.¹⁰

Abbreviations: A-a, alveolar-arterial; ABG, arterial blood gas; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHF, congestive heart failure; CI, cardiac index; CXR, chest x-ray; ECG, electrocardiogram; FEV₁, forced expiratory volume in 1 second; GFR, glomerular filtration rate; INR, international normalized ratio; LFTs, liver function tests; MI, myocardial infarction; PCWP, pulmonary capillary wedge pressure; PFTs, pulmonary function tests; PPCM, peripartum cardiomyopathy; RAP, right atrial pressure; URI, upper respiratory infection; VC, vital capacity.

Transplant-to-conception intervals of more than 2 years were associated with improved mother and newborn outcomes in liver transplant recipients.

> Coscia LA, Constantinescu S, Moritz MJ, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transplant 2009;103–22.

Final decision by Multidisciplinary team with maternal-fetal medicine expert

Timing of pregnancy after transplantation Health-Related quality of life after transplantation

• A meta-analysis of 218 studies, with more than 14,000 transplant recipients

- Overall improvement in all aspects of HR-QOL from pretransplant to posttransplant.
- The overall HR-QOL for transplant recipients was on par with chronically ill patients and remained lower than healthy individuals

Does transplantation produce quality of life benefits? A quantitative analysis of the literature. Dew MA, Switzer GE, Goycoolea JM, et al. Transplantation 1997; 64(9):1261–73.

After successful transplantation, there is a rapid return of fertility. However, in a survey of transplant recipients, 44% were unaware that they could become pregnant posttransplant.

French VA, Davis JS, Sayles HS, et al. Contraception and fertility awareness among women with solid organ transplants. Obstet Gynecol 2013;122(4):809–14.



Pregnancy : Yes or No?

- 31y old
- History of
 - Myocarditis + Pulmonary Embolism
 - Cardio/Respirator Arrest +Prolong Resuscitation
- ESRF —— Renal Transplantation 2y ago (Cre 1.8)
- CHF (Sever LV and RV dysfunction ;EF 16%)
- CVA (residual neurological sequel, hemiparesis)
- IVF for eggs extraction and pundecaut maternity

Question number 2 - Immunosuppression

- To preserve graft function and prevent rejection
- Mainstay immunosuppressive medication
 - Corticosteroids
 - Calcineurin inhibitors- cyclosporine, tacrolimus
 - Antiproliferative agents azathioprine, sirolimus, mycophenolate mofetil
- Difficult to maintain appropriate blood levels during pregnancy (secondary to physiologic changes)
- All immunosuppressive medications have fetal and neonatal risk
 - Increased risk of congenital anomalies (especially sirolimus and mycofenolate mofetil)
 - Premature delivery and IUGR

Immunosuppression

Corticosteroids – Inhibition of leukocyte, macrophage and T-cell activities

Steroid related side effects

- Cushingoid
- HTN
- Adrenal suppression
- Peptic ulcer
- Psychosis
- Glucose intolerance.
- Intra Uterus Gravity Restriction and Preterm Premature Rupture of Membranes
- Cyclosporine, Tacrolimus Inhibition of Calcineurine (<u>Inhibition of T-cell activity</u>)
 - Metabolized in the liver through the P450 system
 - Check maternal blood pressure, blood glucose, Cre and electrolytes
 - Crosses the placenta (50% of maternal level) immunosuppression of fetus





Denton et al. Lancet. 1999;353:1083-1091.

Beaumon Hospital	[•] Tra	nsplant Medication					
	Prograf (Tacrolimus) 0.5mg 1mg 5mg	Anti Rejection Dose varies depending on levels, take at 10am and 10pm. Should be taken on an empty stomach i.e. 1 hour before or 2 hours after food. Do not take prior to blood level being taken on day of clinic visit.					
	Mycolat (Mycophenolate Mofetil) 250mg	Anti Rejection Take 2 caps at 10am and 10pm. Chemist may supply 500mg tab (purple tablet). Dose may be increased by Renal Team. The only brands you should receive are Mycolat or Cellcept if the chemist cannot supply Mycolat.					
2 ²⁸	Septrin (Co-trimoxazole) 480mg	Antibacterial, used to prevent PCP Pneumonia. Take 1 tab at night.					
450	Valcyte (Valganciclovir) 450mg	Anti Viral to prevent CMV infections, not all patients will require this therapy. Dose is dependent upon renal function. Initial dose is usually 1 tablet three times a week. This may increase to one or two tablets once daily as renal function improves.					
	Ranitidine 150mg	To protect the stomach. Certain patients will continue on PPI therapy eg. Lanzaprazole, Omeprazole, and not receive Ranitidine.					
5	Prednisolone 5mg	Steroid Anti Rejection. Take 4 tabs at 10am. Dose will be reduced by Renal Physician after discharge. Also available in enteric coated tablets.					
If unsure please confirm with Transplant Team, Renal Team or Hospital Pharmacist							
training of your individua	I transplant team. If in doubt regardi	nly as an educational teaching tool for transplant recipients. Always follow the advice and ng any medications/doses, please contact your transplant or renal team. N - A guide for patients' for further information					

Question number 3 - Comorbidities

Posttransplantant persist or worsen

- Hypertension
- Diabetes
- Hyperlipidemia

Diabetes

- Postrenaltransplantation pregnant patient 5-9% (*)
- Postlivertransplantation up to 13% Diabetes
- Posthearttransplantation 5-7% Diabetes
- Lung transplant recipient max 27% Diabetes
 - Data of National Transplantation Pregnancy Registry reports





Hypertension

- 25-60% in kidney pregnant recipients
- Up to 35% in liver recipients and Up to 45% in heart recipients
- The worse situation in Lung transplant recipients >55%

• Typical and Atypical signs of infection

- Viral, bacterial, fungal and protozoan
- Hepatitis B and C
- CMV, EBV and Toxoplasmosis

A CONTRACTOR OF CONTRACTOR OF

NATIONAL TRANSPLANT REGISTRY

<u>No specific recommendations (!?) on prophylactic antibiotics before surgical</u> procedures for immunosuppressed patients

Kostopanagiotou G, Smyrniotis V, Arkadopoulos N, Theodoraki K, Papadimitriou L, Papadimitriou J. Anesthetic and perioperative management of adult transplant recipients in nontransplant surgery. Anesth Analg 1999;89:613–22

Armenti VT, Constantinescu S, Moritz MJ, Davison JM. Pregnancy after transplantation. Transplant Rev (Orlando) 2008;22:223–40

Increased Incidence of Obstetric Complication

- Preeclampsia 30% Riley ET. Obstetric management of patients with transplants. Int Anesthesiol Clin 1995;33:125–40
- Preterm labor 36% (liver) and 54% (renal)*
- Cesarean Section 50% (liver) * Casele HL, Laifer SA. Pregnancy after liver transplantation. Semin Perinatol 1998;22:149–55
 53% (renal) loscovich



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J Matern Fetal Neonatal Med, 2014; 27(5): 484–487 © 2014 Informa UK Ltd. DOI: 10.3109/14767058.2013.818973 informa healthcare

ORIGINAL ARTICLE

Peripartum anesthetic management of renal transplant patients – a multicenter cohort study

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16 year 1996-2011 retrospective study ~ 30.000-35.000 deliveries annually







Table 1. Baseline data.		
Total	64 women, 83 labors	
Average maternal age	30.5±5.7 (18-42)	
Average time between	7.5 ± 4.4 (1–20)	
transplantation and labor (years)		
Reason for renal transplantation	Unspecified end-stage renal diseases – 35 (55%)	
•	Glomerulonephritis-9(14%) Reflux nephropathy-7(11%)	
	Amyloidosis-4 (6%)	
	Polycystic kidney–4 (6%) Diabetes mellitus–2 (3%)	
	One case of Wills tumor, hypoplastic kidney and renal dysplasia	
Gestational week	$36 \pm 0.5(25 - 40)$	
Gravity	$2.6 \pm 1.9 (1-10)$	
Parity	0.8 ± 0.3 (0-4) Median range	
Number of renal transplants	59 patients (92.5%)-1 transplant	
in the past	2 patients (3%)–2 transplants	
	1 patient (1.5%)-3 transplants	
	2 patients (3%)-combined renal and	
	pancreas transplant	





J Matern Fetal Neonatal Med, 2014; 27(5): 484-487

Comorbidities	Hypertension 42%	THE JOURNAL OF MATERNAL-FETAL
	Diabetes 12.5%	& NEONATAL MEDICINE
Antirejection medication	Prednisone 99%	
_	Tacrolimus 65%	
	Cyclosporine 54%	
	Imuran 5.4%	
Baseline creatinine (mg/dL)	$1.2 \pm 0.57 (0.4 - 4.1)$	
Baseline hemoglobin	10.2 ± 1.68 (7.1–16)	
(gm/dL)		
Baseline platelets	223.000 ± 83.000 (106-536)	
Baseline white blood cells	$11.900 \pm 5000 (5-13)$	
Numbers expressed as mean ±	standard deviation (range).	

Mode of delivery	NVD 35 (42%) NVD – normal vaginal delivery
	Instrumental delivery 4 (5%)
	Elective cesarean section 35 (42%)
	Emergency cesarean section 9 (11%)
Analgesia for labor	IV analgesia 16 (41%)
	Epidural analgesia 23 (59%)
Anesthesia for CS	Spinal anesthesia 25 (56.8%)
	Combined spinal epidural 2 (4.6%)
	Epidural from labor ward 6 (13.6%)
Ļ	General anesthesia 11 (25%)
Average length of	60 ± 18 (21–120) primary and repeat CS
CS (minutes)	

Reason for CS	10 (23%) - previous CS; 10 (23%) - maternal
	medical condition; 8 (18%) - fetal reasons;
	7 (15%) – obstetric intrapartum reason; and
	9 (21%) – maternal request

Neuraxial Technique for Labor Analgesia and Cesarean Delivery

- Platelet and /or coagulation factor defects secondary to
 - Kidney or liver dysfunction
 - Immunosuppressive therapy (azathioprine, biological agents)
 - Preeclampsia

• TEG (?)

- No guidelines for assessing platelet level and coagulation studies for transplant recipient.
- Patient with normal graft function usually don't need additional laboratory assessment of their coagulation status before initiating NAA

 NARRATIVE REVIEW ARTICLE
 Anesthetic Considerations for the Parturient After Solid Organ Transplantation

Daria M. Moaveni, MD,* Jennifer H. Cohn, MD,* Katherine G. Hoctor, MD,* Ryan E. Longman, MD,† and J. Sudharma Ranasinghe, MD*

(Anesth Analg 2016;123:402–10)

Pregnant patients after liver transplantation Unpublished data from 4 medical centers 1996-2011

Ν	Age	Reason for transplantation	Years between transplantation and labor	Immunosuppressiv e therapy	Steroid therapy
1	40	Fulminant hepatitis	12	No	Yes
2	30	Cirrhosis	5	Cyclosporine	Yes
3 A	21	Wilson's diseases +Hepatitis B	5	Cyclosporine	Yes
3B	26	Wilson's diseases +Hepatitis B	10	Cyclosporine	Yes
4	31	Autoimmune	9	Prograf	Yes
5	32	Hepatitis C	6	Prograf+ Cyclosporine	Yes
6	27	Cirrhosis	3	Prograf	Yes

➢ Age 21-40

- ➤ 3 12y after liver transplantation
- ➤ 100% steroid therapy

Pregnant patients after liver transplantation Unpublished data from 4 medical centers 1996-2011

Ν	GP	Week	Mode of	Anesthesia	Monitoring	Time	Apgar	Neonatal	Blood
		gestation	delivery			of CS	1and	weight	products or
							5min		Complication
1	3/1	38	Vaginal	Epidural	Standard		9/10	2864	No
2	1/1	35	CS	General	Standard	60	8/9	1640	No
3A	1/1	40	Vaginal	Epidural	Standard		9/10	2260	No
3B	3/2	35	Vaginal	Epidural	Standard		9/10	3872	No
4	1/1	36	CS	General	Standard	60	5/10	2395	No
5	4/1	38	Vaginal	Non	Standard		9/9	2850	No
6	3/1	38	CS	Spinal	Standard	50	7/8	2860	No

Hepatic Blood Flow: General versus Regional anesthesia

The analysis of available data suggests that general anesthesia affects the splanchnic and hepatic circulation in various directions and to different degrees. The majority of anesthetics decreases portal blood flow in association with a decrease in cardiac output.

<u>Can J Physiol Pharmacol.</u> 1987 Aug;65(8):1762-79. General anesthesia and hepatic circulation. <u>Gelman S</u>

Vasodilatation Mechanical ventilation

There are no remarkable studies regarding regional anesthesia efficacy in patients with liver disease.

<u>Hepat Mon</u>. 2014 Jul; 14(7): **Anesthesia for Patients With Liver Disease** <u>Poupak Rahimzadeh</u>,



Peripartum/Perioperative monitoring

Review of 69 papers DM Moaveni

ANESTHESIA & ANALGESIA

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- "Standard monitoring is adequate in most cases."
- "Invasive monitoring (IBP or/and CVP) according to risk-benefit ratio."
- "Transthoracic or Transesophageal echography for evaluation of left ventricular filling volume for any patients."

In both our group only one woman (postrenaltransplantation) received IBP (AL) monitoring for CS, secondary to low initial hemoglobin (7.8g/dL) and uncontrolled hypertension.

Blood transfusion concerns



• RBC-antibodies arising from transplanted organs and directed against recipient RBC is a complication of solid organ transplantation.

Ramsey G. Red cell antibodies arising from solid organ transplants. Transfusion 1991;31:76-86

- The blood bank should be contacted early to avoid delays in cross-matching blood
- To avoid leukocyte-related reaction
 - Leukocyte-poor irradiated blood products should be used
 - Modern leukocyte depletion filters remove 99.9% of leukocytes



Toivonen HJ. Anaesthesia for patients with a transplanted organ. Acta Anaesthesiol Scand 2000;44:812–33

Blood transfusion concerns Our data



	Peripartum anesthetic management of renal transpl patients – a multicenter cohort study	lant
Peripartum Blood	4 (6%) patients A. loscovich ¹ *, S. Orbach-Zinger ² *, D. Zemzov ² , A. Reuveni ² , L. A. Eidelman ² , and Y	Y. Ginosar ³
Products	got 1;2;2;2 Paced Red Blood Cells	
	1 – Postpartum hemorrhage	
	2 - Intraoperative bleeding	
	1 – Baseline hemoglobin 7.8 g/dL	
L	Peripartum FluidNormal saline 8 (9%) 1.8L (1–2L)AdministrationRinger lactate 74 (91%) 1.4L (1–2L)	

No blood products in postlivertransplantation group.

Post Lung and Heart transplantation pregnant patients

Table 1. National Transplantation Pregnancy Registry^a: Pregnancies Registered From January 1991^b to December 2014

Solid Organ(s) Transplanted	Recipients	Pregnancles ^c	Live Births
Heart	78	133	91 ^g
Heart-lung	5	5	5
Lung	28	37	22

Data are lacking regarding adaptation of the transplanted lung to pregnancy.

All stress responses are delayed because of denervation.

The risk of rejection, graft loss, and mortality may be higher compared with other solid organ transplants.

Wu DW, Wilt J, Restaino S. Pregnancy after thoracic organ transplantation. Semin Perinatol 2007;31:354–62

- 23:00
- 28y old P3G0 IVF
- 28w Active labor
- H/O Cystic Fibrosis 븆 ESRF
- S/P Lt lung transplantation (in 14y. Old)
- Severe Scoliosis 145cm /~45kg
- Standard monitoring
- One shot spinal
 - 7.5mg Bupivacaine + MO100mcgm
 - IV Ketamine 20mg+20mg
- Baby 800gm → Sepsis → died 2w later

- Pregnant women with solid organ transplants experience
 - Physiologic changes of pregnancy
 - Physiologic changes related to the transplanted graft
 - Side effects of immunosuppressive therapy
- Fetal risks
 - Low birth weigh
 - Prematurity
 - Fetal malformation
- When and how to deliver \implies multidisciplinary team decision

v to deliver 🛶 multic

- Anesthesia
 - Standard monitoring
 - Most women will not have contraindications to NAA
 - Strict aseptic technique Is essential (!!!)
 - AB prophylaxis









Best wishes









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