Reproductive Health in Women Following Abdominal Solid Organ Transplant

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Abstract: Fertility is typically impaired in women with end-stage kidney and liver disease although most women will have restoration of fertility within a year of transplant. Family planning is therefore critical to discuss with reproductive aged transplant recipients in the early post transplant period, in order to ensure timely initiation of contraception, and optimal timing for conception. For women seeking pregnancy the risks to the mother, graft, and baby should be discussed including evaluation of immunosuppression safety and potential for adjusting medications prior to conception. With an increasing number of transplant patients now breastfeeding, immunosuppression safety in lactation continues to carry great importance.

Fertility in the pre- and post-transplant setting

End stage renal disease (ESRD) and end stage liver disease (ESLD) are associated with impaired fertility in women. Nearly three quarters of women listed for liver transplant have secondary amenorrhea, with cessation of menstrual cycles in the setting of progressive liver disease.*(1)* Similar patterns have long been noted in women with ESRD with more than 90% of women on dialysis having irregular or absent menstrual cycles.(2) Although the exact etiology leading to impaired fertility is not known, both disease states are characterized by dysregulation in the hypothalamic-pituitary-ovarian (HPO) axis with abnormal increase in prolactin secretion from the pituitary gland. Prolactin inhibits gonadotropin-releasing hormone (GnRH), impairing the pulsatile release of FSH and LH, which is critical for ovulation. The HPO dysregulation is further exacerbated in ESRD by impaired renal clearance of prolactin. After liver and kidney transplant, hormonal levels normalize (1, 3), and the majority of women will resume

regular menstrual cycles within one-year post transplant, though menses may resume as early as one-month post transplant. The earliest pregnancy has occurred within one first month after liver transplant (LT), highlighting the importance of reproductive counseling and family planning in the initial post transplant period.

Contraception in Transplant Recipients:

As the majority of women awaiting transplant are amenorrheic, pregnancy concerns and restored fertility may not come to mind. In a U.S. study of reproductive-aged kidney transplant (KT) and LT recipients, only half of women used any form of contraception, and 44% were not aware that pregnancy was possible after transplant.(4) In another study of KT/LT recipients nearly half were using no contraception, and ~ 40% of women were relying upon high failure methods such as condoms, rhythm, or withdrawal.(5) Among women who conceived posttransplant, more than a third had unplanned pregnancies. It is therefore important that transplant providers discuss family planning in the early transplant period to ensure timely initiation of effective methods.

Intrauterine devices (IUDs)

Intrauterine devices (IUDs), including copper (ie Paraguard®) or hormonal (ie Skyla® or Mirena®), are among the most effective contraceptive methods available. According to the Centers for Disease Control (CDC), failure rates in the general population are < 1% (0.8% for copper IUDs and 0.2% for hormonal), which contrasts with high failure rates of non-hormonal methods such as condoms (18%), rhythm (24%), or withdrawal (22%). Copper IUDs may be used for up to 12 years, and result in localized inflammation that creates a hostile environment for the survival of sperm. As copper IUDs are non hormonal, women maintain regular menstrual cycles. Menstrual bleeding with the copper

IUD is often heavier, which is less ideal for women with existing posttransplant anemia. Hormonal IUDs are effective for 3-5 years, depending on the specific brand, and often result in lighter and less frequent menses.

Concerns surrounding the use of IUDs stemmed from a 1980s case report of two adolescent KT recipients who became pregnant while using the copper IUD.(6) It was postulated that immunosuppression (IMS) may lower the inflammatory response needed for IUD efficacy. However, the local inflammatory response of IUDs is a macrophage driven process, therefore not affected by transplant IMS.(7) The largest study in the transplant population included 647 KT recipients, 178 of whom were using IUDs. While 15% of the cohort had an unwanted pregnancy, no pregnancies occurred in the IUD group.(8) Similar results were reported in KT and LT recipients using hormonal IUDs, with no pregnancies in 3 years of follow-up.(9-11) Current IUDs are also well studied in immunosuppressed women, and have no greater risk of pelvic inflammatory disease (PID) than in the general population of non-IUD users.(12, 13) There have been no cases of PID among > 200 KT and LT recipients with published IUD use to date.(6, 8, 9, 11)

Combined hormonal contraception (CHC)

CHC contains estrogen and progestin, and works primarily by impairing ovulation. Delivery methods include oral contraceptive pills (OCPs), the transdermal patch, and vaginal ring. Failure rates are ~ 9%, therefore higher than that of IUDs. Safety concerns in the general population include risk of venous thromboembolism, stroke, and elevated blood pressure. These agents are metabolized by cytochrome P450 therefore medications that induce P450, may reduce their efficacy. Older formulations were commonly associated with liver enzyme elevation, though current agents carry only rare

risk of cholestatic liver injury.(14) There are no controlled studies evaluating side effects in transplant patients.(15) In an uncontrolled study of 36 KT recipients using OCPs or the patch approximately one third required increased blood pressure medication, 1 developed thrombophlebitis, and another had graft failure 10 years post transplant.(16) In a 1-year follow-up of 16 LT recipients no embolic events or elevated blood pressure was noted.(17)

Progestin-only agents

Progestin only contraception does not carry increased risk of hypertension or VTE, though the failure rate is still ~9%. Depo-provera is an intramusclular injection given every 12 weeks, with a failure rate of ~6%. Unfortunately a black box warning was issued by the Food and Drug Administration (FDA) in 2004 given associated decline in bone mineral density. Although bone density normalizes with discontinuation (18) there are lingering concerns for transplant patients given baseline osteomalacia in the setting of renal disease, and the additional risk of osteopenia related to post transplant steroid use. The subcutaneous implant (ie Nexplanon®) is not associated with bone loss, though no studies have evaluated its use in transplant patients. In the general population the implant carries the lowest failure rate of all hormonal agents (0.05%).

In 2013, the CDC published the *U.S. Selected Practice Recommendations for Contraceptive Use* (U.S. SPR) and includes formal recommendations for contraceptive use in solid organ transplant, which are graded as: 1 = No restriction, 2 = Benefits outweigh theoretical or proven risks, 3 = Risks outweigh benefits, and 4 = Unacceptable risk (Figure 1). These recommendations are separately provided for stable or complicated

graft function (the latter defined as acute or chronic graft failure, rejection, or cardiac allograft vasculopathy). All hormonal methods are considered safe in women with stable grafts. Only progestin-only agents have a favorable safety grade “2” although these recommendations have not incorporated additional larger studies also demonstrating favorable IUD safety data.(11, 19) The CDC does note that with graft dysfunction existing IUDs may be left in place. CHC carries an unacceptable risk for complicated graft function, and should be discontinued. We consider IUDs first line for KT and LT patients with both complicated and uncomplicated graft function given their favorable safety and efficacy data.

Pregnancy outcomes in transplant recipients

For reproductive aged women seeking pregnancy after transplant, timing is key. In 2005 the American Society of Transplantation issued a consensus statement advising deferral of pregnancy for at least one year after solid organ transplant.(20) Delaying pregnancy helps to ensure stable graft function with the lowest levels of immunosuppression, and therefore also lowest risk of infectious complications.(21) When considering pregnancy, recipients and providers should be aware of potential risks, including risks to the graft, as well as risks to the baby. Pregnancy in the setting of solid organ transplant is higher risk, although with coordinated care among the various specialists, the majority of KT and LT recipients (~ 75%) will have successful deliveries.(22, 23)

A higher proportion of transplanted women are delivered by caesarean section than non-transplant recipients.(22, 23) The type of delivery should be guided by obstetric indications, rather than history of transplant. Vaginal delivery is not contraindicated in women with LT or KT, nor do their previous surgical procedures affect uterine expansion. There is potential for inadvertent renal allograft damage during caesarean

section therefore knowledge of its anatomical location is required by obstetricians prior to surgical delivery.

Maternal/graft risks

Hypertension during pregnancy is more common in transplant patients than in non-transplant controls (24), due in part to the hypertensive side effects of immunosuppressive agents. As the majority of transplant recipients require lifelong immunosuppression, the Transplant Pregnancy Registry (TPR) International (formerly the National Transplantation Pregnancy Registry), was established in 1991 to study pregnancy outcomes in all sold-organ transplant recipients. Listed in Table 1 are the pregnancy outcomes reported to the TPR in KT and LT recipients. Hypertension in pregnancy is twice as common in KT as compared to LT recipients (22, 23) (Table 1), which likely relates to longstanding hypertension prior to transplant leading to chronic endothelial damage. Diabetes is also more common in KT recipients prior to transplant, and given greater immunosuppression (IMS) needs in KT recipients, their risks of HTN and DM may be exacerbated by IMS-related side effects. Prevalence of gestational diabetes is also higher in KT recipients at ~ 8%, compared to 5% in LT recipients, and < 4% of non transplant controls.(25) This would be detected during routine pregnancy care.

Whether pregnancy increases risk of rejection or graft loss remains controversial. The prevalence of rejection during pregnancy in the TPR is reported at 0.9% for KT and 3.4% for LT patients, with a prevalence of 1.4% and 4.2% respectively in the first 3 months post partum (Table 1). Graft loss within 2 years of transplant is 5.9% in KT and 3.5% in LT patients, neither of which are greater than in non-pregnant controls. Data from the United Kingdom (UK) demonstrate lower acute cellular rejection episodes in women

conceiving at > 12 months compared to < 12 months post LT (11% vs 46%, respectively, p=0.001),(26) highlighting the importance of stable graft function prior to conception. A recent analysis of US Medicare data described elevated rates of graft loss with conception up to 24 months after KT.(27) Pre-existing hypertension and severity of graft dysfunction prior to conception have been shown to be independently associated with graft failure in KT recipients.(28-30) Complicating this relationship between pregnancy and rejection is the potential need for increased tacrolimus dosing during pregnancy. Tacrolimus is highly protein bound, and concentrated within red blood cells (RBC). Increased total body water dilutes RBC counts and albumin, affecting tacrolimus levels. While total tacrolimus concentrations decline in pregnancy, it is uncertain whether there is disproportionate reduction in bound versus free tacrolimus levels.(31) One study reported need for 20-25% increased dose to maintain target levels(32), though over aggressive increase in tacrolimus during pregnancy may lead to tacrolimus toxicity..

Fetal/Infant risks

Transplant recipients are at increased risk for developing pre-eclampsia. Pre-eclampsia is more common in KT than LT recipients, although in both populations the prevalence of is ~ 5 times greater than in non-transplant controls.(22-24). Pre-eclampsia in transplant recipients may contribute to their increased rate of cesarean deliveries and higher prevalence of pre-term births. Aspirin use is often advised during pregnancy to reduce their risk of pre-eclampsia.

Immunosuppression and fetal outcomes

In 2015 the FDA began replacement of former pregnancy risk letter categories (ie A, B, C, D and X) with revised labeling including dosing, potential fetal risks, and registry outcome data. In the following section, pregnancy outcomes by IMS will be therefore be

discussed in broad categories based on available evidence, including: 1.“Generally considered safe”-ie calcineurin inhibitors (cyclosporine and tacrolimus), prednisone and azathioprine; 2.”Contraindicated during pregnancy” -ie mycophenolate mofetil and mycophenolic acid, 3. “Not enough information” -ie sirolimus, everolimus, and belatacept.

Calcineurin Inhibitors

The calcineurin inhibitors (CNIs) cyclosporine and tacrolimus are the cornerstone of modern IMS, and commonly used in pregnancy. Early concerns regarding increased risk of birth defects with cyclosporine and tacrolimus have not been demonstrated in larger studies, and rates of birth defects in women using CNIs are similar to the general population(25, 33). Although a higher incidence of prematurity and low birthweight have been reported in offspring of mothers using CNIs, although this finding could relate to underlying comorbidities in transplanted mothers, rather than CNI-related side effects.

Mycophenolic Acid Products (MPAs)

MPAs including mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS), carry the greatest known risks to the developing fetus. Spontaneous abortions occur in ~ 45% of women using this agent at the time of conception, and approximately 22% of children born to mothers using MPAs have developmental anomalies (34, 35). Birth defects associated with MPA use include oral-facial, esophageal, cardiac, and renal abnormalities, as well as microtia, a defect in the development of the external ear that is more specific to MPA exposure.(36) For women seeking pregnancy, strategies such as temporary replacement of MPA with azathioprine along with adding or increasing prednisone should be considered. This strategy is not associated with increased risk of acute rejection during pregnancy or postpartum

period(37). Compared to KT recipients who remain on MPA in early pregnancy, those that discontinue MPA preconception have more live births, with an incidence of birth defect that is similar to the general population (Table 2).(37) Women of childbearing potential should use two forms of highly effective contraception while taking MPA, and discontinue this agent at least 6 weeks prior to conceiving. Providers should report patients that have conceived while using MPA, or within 6 weeks of stopping this agent, to the Mycophenolate Risk Evaluation and Mitigation Strategy (REMS), an FDA mandated program that collects pregnancy outcome data and provides patient and provider education.(38)

Azathioprine

Azathioprine has not been associated with increased risk of fetal anomalies in humans.(39, 40) While preterm delivery and fetal growth restriction have been noted, this may be attributable to maternal comorbidities and not necessarily a drug-related side effect. Transplant recipients are often switched from MPA products to azathioprine in preparation for conception. One study of n=69 recipients (n= 46 KT and no LT recipients) switched to MPA at least 6 weeks prior to conception found no increased risk of spontaneous abortions or birth defects as compared to those who did not switch MPA prior to pregnancy.(41) Azathioprine is therefore considered a safe IMS option in pregnancy.

Prednisone

Prednisone at maintenance dose is generally considered safe in pregnancy. A meta-analysis of non-transplant women using corticosteroids in the first trimester found no higher rate of major anomalies. A prior report of cleft palate in children exposed to in utero steroids was not confirmed in follow-up studies.(42, 43)

Sirolimus and Everolimus

In animal studies, in utero sirolimus exposure results in decreased fetal weights, delayed ossification and increased fetal mortality. However, no malformations have been noted in human case reports to date.(44) TPR data of n=19 sirolimus exposed women identified 2 with birth defects.(25) There have been 2 reported KT recipients and 2 heart transplant recipients with everolimus use in the first trimester. Outcomes included 5 live births, 1 birth defect, and 1 miscarriage.(25) Given the small number of reports, definitive recommendations about the safety of sirolimus and everolimus in pregnancy cannot yet be provided.

Belatacept

In the TPR there have been 2 reported KT recipients taking belatacept throughout 3 pregnancies. The first had two unplanned pregnancies, one 11-week miscarriage (concomitant MPA exposure for the first 3 weeks) and one healthy infant. The second recipient had a planned pregnancy, switched from MPA to azathioprine ~ 1 month pre-conception, and delivered a healthy infant. Both recipients had normal graft function at last TPR follow-up.(25) There are no additional reports of belatacept use in pregnancy, therefore its use cannot be recommended.

<u>Breastfeeding After Transplant:</u>

Breastfeeding has substantial benefits to mother and child and for the general population, the American Academy of Pediatrics (AAP) advises exclusive breast-feeding for the first 6 months of life.(45) Within the transplant setting, the number of women that choose to breastfeed continues to grow (Figure 2). While IMS during breastfeeding could

potentially render the mother and infant more susceptible to infections, formal studies of these risks have not been conducted.

The AAP previously provided breastfeeding recommendations by drug exposure, but now advises patients and practitioners to consult the online LACTMED database.(46) LACTMED is maintained by the National Institutes of Health and uses updated registry and literature reviews to provide pharmacokinetic information and safety recommendations. Corticosteroids have long been considered safe by the AAP with ongoing data from LACTMED supporting its use in nursing. In one study, the concentration of corticosteroids within the breastmilk of women taking 10-80 mg of prednisolone per day was between 5-25% of maternal serum concentrations. Azathioprine is also considered safe in breastfeeding, with safety data deriving from both the transplant setting and women with inflammatory bowel disease.(46, 47) At doses up to 200 mg per day there is low to unmeasurable active metabolites identified in breastmilk or infant blood.(48) There have been no reported adverse effects on immunity, infection or growth in children followed up to 3.5 years, though longer follow-up data are lacking.(49) Cyclosporine and tacrolimus are both measurable in breastmilk, although in small quantities that are unlikely to cause harm to nursing infants. In a study of six exposed infants, only one had detectable cyclosporine concentrations and had normal development up to one year.(50) Estimated infant exposure to weight adjusted maternal cyclosporine dose is 0.33%.(51) Similarly estimated infant exposure when breastfed by mothers taking tacrolimus is low (0.23%). One study found that infant tacrolimus concentrations were lower than maternal concentrations after delivery and became undetectable by two weeks postpartum, regardless if they were bottle or breastfed.(52) Therefore CNIs are also likely safe for nursing.(46) In contrast,

breastfeeding while using MPAs, everolimus or sirolimus is not recommended given lack of data on drug excretion in breast milk.

Summary: The majority of reproductive aged women will have restoration of fertility following kidney and liver transplant, which may occur within weeks to months of their surgery. Family planning should be discussed at the first post-operative visit to ensure timely initiation of contraception. Counseling must also include a discussion of pregnancies desires to ensure that conception is planned at a time that is safest for both the mother and baby. Pregnancy in the setting of solid abdominal organ transplant is higher risk than in the general population, and includes increased risk of diabetes, hypertension, as well as complications such as pre-eclampsia. Nonetheless, most transplant recipients will have successful deliveries with healthy offspring. Immunosuppressive medications must be tailored for conception plans to ensure use of regimens that provide optimal graft outcomes while minimizing infant risk. A growing number of transplanted women are enjoying the benefits of breastfeeding, though lactation safety based on immunosuppression must be discussed. With these goals in mind, transplant providers can help to optimize the health of pregnant mothers, their allografts, and their infants.

	Kidney			Liver			
Female Recipients	1031			257			
Mean age at 1st transplant (yrs)	24 ± 6			21 ± 9			
Pregnancies	1867			487			
Mean transplant-conception interval (yrs)	5.3 ± 4			7.6 ± 6.5			
Unplanned	39%			41%			
Estimated conception range	July 1967 – June 2016			Nov 1985 – Feb 2016			
During Pregnancy							
Primary Immunosuppressant[1]	CsA	Tac	Other	CsA	Tac	Other	None
	46%	29%	25%	39%	57%	<1%	3%
MPA exposure	8.2%			5.5%			
Sirolimus exposure	1.3%			1.6%			
Azathioprine exposure	72%			22%			
Hypertension treated	55%			23%			
Diabetes treated	8%			8%			
Preeclampsia	30%			21%			
Rejection[2]	0.9%			3.4%			
After Pregnancy							
Postpartum rejection[2]	1.4%			4.2%			
Graft loss within 2 yrs of pregnancy outcome	5.9% (110 losses)			3.5% (17 losses)			
OUTCOMES[3]	1932			502			
Live births	75%			73%			
Neonatal deaths	1.5%			1.1%			
Miscarriages	18%			22%			
MPA exposure[4]	15.3%			17%			
Stillbirths	2%			1%			
Ectopic pregnancies	1%			1%			
Terminations	4%			4%			
LIVE BIRTHS	1453			364			
Mean gestational age (wks)	35.9 ± 3.4			36.6 ± 3.4			
Premature (<37 wks)	50%			39%			
Early Preterm (<34 wks)	20%			16%			
Mean birth weight (g)	2572 ± 764			2740 ± 787			
Low (<2500 g)	42%			30%			
Very Low (<1500 g)	10%			8%			
Cesarean section	53%			46%			
Birth Defects	4.4%			4.7%			
Child follow-up (yrs)	14.1 ± 9.6			9.1 ± 7.1			
Recipient follow-up (yrs)	14.8 ± 9.7			10.3 ± 7.4			
Maternal deaths	18.8%			14%			
Mean age of child at maternal death (yrs) Number of children	16.4 ± 8 237 children			10.4 ± 6.5 43 children			
Adequate graft function at last follow-up	67%			81%			

[1] cyclosporine or its modified form (CsA); tacrolimus (Tac); sirolimus, everolimus, mycophenolic acid products, or belatacept (other); mycophenolic acid products (MPA); [2] biopsy-proven treated acute rejection; [3] includes multiple births; 4 % of miscarriages with reported 1st trimester MPA exposure

(TPR Annual Report 2016)

Table 2 Pregnancy outcomes in kidney transplant recipients by pre-pregnancy Mycophenylate Product (MPA) cessation in the Transplant Pregnancy Registry

	MPA exposure during pregnancy	**MPA discontinued pre-conception**	**p value**
Recipients/Pregnancies	**96/142**	**188/302**	
Unplanned pregnancies	59%	15%	<0.001
Conception Age (yrs)	29.1±4.6	31.9±4.6	<0.001
Transplant to conception interval (yrs)	3.9±2.8	5.6±3.7	<0.001
Creatinine before pregnancy (mg/dL)	1.3±0.4	1.1±0.3	<0.001
Creatinine during	1.4±0.8	1.2±0.6	0.006
Creatinine postpartum	1.5±0.8	1.2±0.5	<0.001
Biopsy proven acute rejection during	4.3%	1.3%	0.08
Biopsy proven acute rejection postpartum	5.1%	1.4%	0.04
Pregnancy Outcomes			
Live births	48%	78%	<0.001
Miscarriages	48%	20%	<0.001
Stillbirths	1%	1%	NS
Ectopic pregnancies	0	1%	NS
Terminations	3%	0.3%	NS
Live births	69	246	
Mean gestational age (wks)	35.3±3.3	35.7±3.5	NS
Premature (<37 wks)	55%	48%	NS
Mean birthweight (g)	2406±759	2549±756	0.07
Low birthweight (<2500 g)	49%	39%	NS
Birth defects (live born)	11.6%*	5.7%	NS

**Includes 61% MPA-related defects. Percentage does not include MPA-related defects found in 1 stillbirth and 1 termination.*

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