

## CHAPTER 9

# Report from the National Transplantation Pregnancy Registry (NTPR): Outcomes of Pregnancy after Transplantation

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In May 1956, identical twin females were evaluated for transplantation and after a successful kidney transplant that year with one twin donating to the other, the recipient became pregnant and delivered a baby on March 10, 1958. Dr. Joseph Murray and his group (1) subsequently reported this first successful pregnancy in a transplant recipient in 1963. Further experience in this field has been gained through continued case reports, center reports, and registry data.

The National Transplantation Pregnancy Registry (NTPR) was established in 1991 to study the outcomes of pregnancies in transplant recipients in North America, including female transplant recipients who have had pregnancies and male transplant recipients who have fathered pregnancies. All pregnancy outcomes are analyzed including livebirths, spontaneous abortions, therapeutic abortions, stillbirths and ectopic pregnancies.

*Table 1. Pregnancies in female transplant recipients reported to the NTPR.*

Organ	Recipients	Pregnancies	Outcomes*
Kidney	716	1,097	1,125
Liver	111	187	189
Liver-Kidney	4	6	7
Pancreas-Kidney	38	56	58
Heart	33	54	54
Heart-Lung	3	3	3
Lung	14	15	15
Totals	919	1,418	1,451

\* Includes twins and triplets

The data also include the follow-up of parents and offspring to determine if there are any long-term effects of pregnancy for the recipient, graft or long-term sequelae for the offspring. This report reviews data collected and analyzed by the NTPR over the past 14 years. This chapter also includes 7 personal accounts of transplant recipients and their experience with a post-transplant pregnancy or in one case fathering a pregnancy. This represents the first NTPR report since the registry relocated to Temple University School of Medicine; additional entries for this year are in progress and will be reflected in future chapters.

## METHODS

The study method includes a single-page questionnaire with a consent form. The questionnaires are completed by transplant recipients who are identified by their coordinators, physicians, or who self-report to the registry. Consent allows for telephone contact with the recipients and for access to medical records for parent and child. Periodic follow-up is conducted via telephone interviews with the recipient and transplant centers, and by review of medical records. An honorarium is provided to health professionals for initial registration and follow-up.

## RESULTS

Tables 1 and 2 show the number of completed entries into the NTPR as of January 2005 totaling 1,418 pregnancies in 919 female recipients and 1,020 preg-

nancies fathered by 704 male recipients. The following sections detail each pregnancy by transplanted organ group for female recipients and for male recipients who have fathered pregnancies, emphasizing analyses completed over the past year.

### Female Kidney Recipients

Table 3 compares the outcomes of female kidney recipients on Sandimmune® (CsA)-, cyclosporine modified, USP, (Neoral® and Gengraf®), and tacrolimus-based regimens. The largest group reported to the NTPR is still the Sandimmune kidney recipient group but outcomes are accruing for Neoral® and tacrolimus pregnancies. Overall, outcomes are not markedly different among the

*Table 2. Pregnancies fathered by male transplant recipients reported to the NTPR.*

Organ	Fathered		
	Recipients	Pregnancies	Outcomes*
Kidney	526	784	796
Liver	54	71	76
Liver-Kidney	2	4	4
Pancreas-Kidney	28	34	35
Heart	91	123	125
Heart-Lung	1	2	2
Lung	2	2	2
Totals	704	1,020	1,040

\* Includes twins and triplets

*Table 3. Pregnancy outcomes in female kidney transplant recipients reported to the NTPR.*

	CsA	Neoral®	tacrolimus
<b>Maternal Factors</b>			
Transplant to conception interval (mean)	3.3 yrs	5.2 yrs	3.3 yrs
Hypertension during pregnancy	62%	72%	58%
Diabetes during pregnancy	12%	3%	10%
Infection during pregnancy	23%	22%	34%
Rejection episode during pregnancy <sup>1</sup>	4%	2%	4%
Pre-eclampsia	29%	31%	29%
Mean serum creatinine (mg/dL)			
Before pregnancy	1.4	1.4	1.2
During pregnancy	1.4	1.4	1.5
After pregnancy	1.6	1.5	1.5
Graft loss within 2 yrs of delivery	11%	4%	13%
<b>Outcomes (n)<sup>2</sup></b>	<b>(496)</b>	<b>(154)</b>	<b>(71)</b>
Therapeutic abortions	8%	1%	1%
Spontaneous abortions	12%	19%	24%
Ectopic	1%	0%	0%
Stillborn	3%	1%	3%
Livebirths	76%	79%	71%
<b>Livebirths (n)</b>	<b>(376)</b>	<b>(121)</b>	<b>(50)</b>
Mean gestational age	36 wks	36 wks	35 wks
Mean birthweight	2,493 gms	2,448 gms	2,378gms
Premature (<37 wks)	52%	54%	53%
Low birthweight (<2,500 gms)	46%	50%	50%
Cesarean section	51%	46%	55%
Newborn complications	41%	50%	54%
Neonatal deaths n (%)	3 (1%)	0	1 (2%)
(within 30 days of birth)			

<sup>1</sup> Rejection for CsA including chronic rejection; Neoral® and tacrolimus biopsy proven acute rejection only; <sup>2</sup> includes twins, triplets; CsA - Sandimmune® brand cyclosporine (321 recipients, 486 pregnancies); Neoral® brand cyclosporine (109 recipients, 146 pregnancies); tacrolimus (56 recipients, 70 pregnancies)

*Table 4. Pregnancy outcomes of female kidney recipients with mycophenolate mofetil (MMF) or sirolimus exposure during pregnancy reported to the NTPR.*

Case No.	Regimen <sup>1</sup>	Outcome <sup>2</sup>	Birthweight (gms)	Gestational Age (wks)
1	MMF, tacro, prednisone	L	2,240	34
2	MMF, tacro, prednisone	SA	N/A	7
3	MMF, tacro, prednisone	L	822	31
4	MMF, tacro, prednisone	L	1,701	35
5	MMF, Neoral®, prednisone	L	2,495	36
		SA	N/A	7
		SA	N/A	6
		L	2,977	36
6	MMF, Neoral®, prednisone	SA	N/A	8
		L	2,240	35
7	MMF, tacro, prednisone, sirolimus (see text)	L	1,531	31
8	MMF, Neoral®, prednisone	L	3,118	39
9	MMF, tacro, prednisone	SA	N/A	4
		L	2,211	33
10	MMF, tacro, prednisone	SA	N/A	5
11	MMF, tacro	SA	N/A	4
		SA	N/A	5
12	MMF, tacro	L	3,118	38
13	MMF, Gengraf®, prednisone	SA	N/A	9
			N/A	6
			N/A	7
14	Sirolimus, tacro, pred	SA	N/A	8
15	Sirolimus, Neoral®, pred	L	2,637	36
16	Sirolimus, Neoral®, pred	L	3,076	38

<sup>1</sup> tacro = tacrolimus; <sup>2</sup> L = Livebirth, SA = Spontaneous Abortion

groups analyzed. One case has been reported of a recipient on a tacrolimus-based regimen with a neonatal death due to cardiomyopathy (2). There were no other neonatal deaths reported among the newer entries related to cardiomyopathy. As the number of recipients on generic versions of cyclosporine grows, further analyses will follow.

Three recipients have reported 5 pregnancies while taking Gengraf®. One recipient was maintained on Gengraf®, prednisone and mycophenolate mofetil (CellCept®, MMF) (see below and Table 4) and reported 3 spontaneous abortions. The other recipients each reported a livebirth with a mean gestational age of 38 weeks and a mean birthweight of 3,076 grams. There were no rejections during pregnancy or within 3 months postpar-

tum. All 3 recipients reported adequate graft function at last follow-up.

MMF exposure has been reported to the registry by 13 female kidney recipients with 21 pregnancies (10 livebirths, 11 spontaneous abortions) (Table 4). Exposures were varied as MMF dosages during pregnancy may have been decreased or discontinued. Case number 1 was a recipient who received her second kidney transplant at approximately 3 weeks gestation, with the initiation of MMF, tacrolimus and prednisone. At 26 weeks the pregnancy was discovered; MMF was decreased from 1,000 to 500 mg BID. The child was noted to have hypoplastic nails and shortened fifth fingers but was healthy and developing well at last follow-up (age 6 years) (3). In case number 7, conception occurred while the mother

**Table 5.** Birth defects reported to the NTPR in offspring of female kidney recipients taking Neoral®- or tacrolimus-based regimens during pregnancy.

Defect	(n)	Regimen
Cleft lip and palate, ear deformity	1	tacro, MMF then sirolimus, pred
Hypoplastic nails and shortened fifth fingers	1	tacro, MMF, pred
Renal cystic dysplasia	1	tacro alone
Submucous cleft palate	1	Neoral®, aza, pred
Tongue tied	1	Neoral®, aza, pred
Pyloric stenosis	1	Neoral®, aza, pred
Imperforate anus, clubbed feet, hypospadias	1	Neoral®, aza, pred
Total number of liveborn with birth defects	7/171 (4%)	

*Tacro=tacrolimus; MMF=mycophenolate mofetil; pred=prednisone; aza=azathioprine*

was maintained on MMF, tacrolimus and prednisone. At 24 weeks, a biopsy proven acute rejection occurred, the mother required dialysis, and the rejection was treated with steroids and antithymocyte globulin (Thymoglobulin®); sirolimus (Rapamune®) was also started. The newborn was reported to have a cleft lip and palate (repaired surgically), and an ear deformity (microtia). The remaining 8 children had no birth defects reported.

Four kidney recipients with exposure to sirolimus during pregnancy, reported 4 pregnancies (including case 7 above; 3 livebirths and one spontaneous abortion).

Except for case 7, no structural malformations were reported in the other 2 livebirths.

Listed in Table 5 are the structural malformations reported in the offspring of kidney recipients maintained on Neoral® or tacrolimus. For comparison, the incidence of malformations in the NTPR Sandimmune® group was 18/362 (5%) (4).

### Female Liver Recipients

Table 6 summarizes the 111 NTPR female liver recipients with 187 pregnancies and 189 livebirths. In a recent analysis, we examined 31 pregnancies of 16 fe-

**Table 6.** Pregnancy outcomes in female liver transplant recipients reported to the NTPR.

<b>Maternal Factors</b>		Neonatal deaths n (%)	0%
Transplant-to-conception interval	4.3 yrs	(within 30 days of birth)	
Hypertension during pregnancy	35%	<b>Immunosuppression by pregnancy<sup>2</sup></b>	<b>n (%)</b>
Diabetes during pregnancy	5%	No immunosuppression	5 (3%)
Infection during pregnancy	27%	CsA, aza and prednisone	51 (27%)
Rejection episode during pregnancy	8%	CsA and prednisone	40 (22%)
Pre-eclampsia	23%	CsA and aza	1 (1%)
Graft loss within 2 yrs of delivery	7%	CsA	3 (2%)
<b>Outcomes (n)<sup>1</sup></b>	<b>(189)</b>	Neoral®, aza, and prednisone	10 (5%)
Therapeutic abortions	6%	Neoral® and prednisone	15 (8%)
Spontaneous abortions	19%	Neoral® and aza	2 (1%)
Ectopic	0%	Neoral®	7 (4%)
Stillbirth	2%	Tacrolimus, aza and prednisone	7 (4%)
Livebirths	73%	Tacrolimus and aza	2 (1%)
<b>Livebirths (n)</b>	<b>(138)</b>	Tacrolimus and prednisone	27 (15%)
Mean gestational age	37 wks	Tacrolimus, MMF and pred	1 (1%)
Premature (<37 wks)	36%	Tacrolimus and MMF	1 (1%)
Mean birthweight	2,705 gms	Tacrolimus	12 (7%)
Low birthweight (<2,500 gms)	34%	Gengraf® and aza	1 (1%)
Cesarean section	35%	Gengraf®	1 (1%)
Newborn complications	29%		

<sup>1</sup> includes twins; <sup>2</sup> one pregnancy unknown regimen

male liver recipients with autoimmune hepatitis as their primary diagnosis. There were 18 livebirths (58%), 12 spontaneous abortions (39%), one therapeutic abortion (3%) and no ectopic pregnancies or stillbirths. The transplant to conception interval was  $3.5 \pm 2.8$  yrs. Immunosuppression during pregnancy was cyclosporine based in 16 (Sandimmune® 15, Neoral® 1), tacrolimus based in 14, and included prednisone in 29 pregnancies. The comorbid conditions reported during pregnancy were: hypertension 10/31 (32%), infections 9/28 (32%), pre-eclampsia 6/22 (27%), and diabetes 2/31 (6%). Biopsy-proven acute rejection occurred in 3/31 (10%) compared to 11/152 (7%) liver recipient pregnancies with other initial diagnoses. One recipient had had recurrent autoimmune hepatitis postpartum and another biopsy-proven acute rejection postpartum. The mean gestational age for the 18 livebirths was  $36.6 \pm 3.4$  wks and their mean birthweight was  $2,645 \pm 635$  gms. At last follow-up, all 18 children were reported healthy and developing well.

Follow-up of maternal graft function of the recipients transplanted for autoimmune hepatitis was as follows: 12 recipients reported adequate function, one of whom lost her graft 1.7 years postpartum and had a successful liver-kidney transplant; 2 recipients reported reduced function; one recipient died from complications after a liver biopsy; one recipient was lost to follow-up. By comparison, 7/91 (8%) graft losses were reported within 2 years of pregnancy in the other NTPR female liver recipients. Female liver transplant recipients with autoimmune hepatitis had successful pregnancies after transplantation that were comparable to liver recipients with other diagnoses, although additional study is warranted. Pregnancy did not appear to have a negative impact on maternal survival in this group.

Among the liver recipients, 2 were reported last year with MMF exposure during pregnancy. Both conceived while on MMF and tacrolimus (one continued MMF; the other discontinued MMF when the pregnancy was discovered) and delivered healthy infants; at last follow-up the children were healthy and developing well. No structural malformations were reported in either child.

### ***Female Liver-Kidney Recipients***

Four recipients reported 6 pregnancies with 7 outcomes (one set of twins) after liver-kidney transplant. One of these recipients has had 3 pregnancies, including the twins. A new entry reported is a woman transplanted for oxalosis who first received a living-unrelated donor liver

and then 8 months later a kidney from a different living donor. She was maintained on tacrolimus and prednisone and conceived 5 years after transplantation. At 37 weeks she delivered a healthy infant weighing 2,792 grams. At last follow-up mother and infant were doing well 4 months postpartum. The recipient chose to breastfeed her baby with no reported problems due to breastfeeding.

### ***Female Pancreas-Kidney (P/K) Recipients***

Listed in Table 7 are the 38 female P/K recipients who have reported 56 post-transplant pregnancies with 58 outcomes. The mean transplant to conception interval was  $3.7 \pm 2.4$  yrs. Maintenance immunosuppression during pregnancy was cyclosporine based in 43 (25 Sandimmune®, 16 Neoral®, 2 Gengraf®) and tacrolimus based in 13. Maternal comorbid conditions during pregnancy included: hypertension 75%, infections 55%, and pre-eclampsia 34%. Only one recipient reported gestational diabetes; regular insulin coverage was started at 24 weeks but was discontinued postpartum. Rejection occurred during 3 pregnancies; all 3 recipients went on to lose their grafts.

There were 46 liveborn among the P/K recipients; 25 were delivered by cesarean section. One cesarean section was complicated by a tear to the duodenal portion of the graft and required repair. The mean gestational age of the 46 liveborn was  $34 \pm 3.1$  wks; 35 (78%) were premature (<37 wks). Their mean birthweight was  $2,096 \pm 721$  gms and 29 (63%) were low birthweight (<2,500 gms). By comparison and depending upon immunosuppressive regimen, in kidney-only recipients reported to the registry, the mean gestational age for newborns was 35 to 36 wks, with birthweights of 2,378-2,493 gms. Twenty-six (57%) infants of P/K recipients had neonatal complications with one neonatal death from sepsis in a severely premature infant. Although the P/K offspring have lower mean gestational ages and birthweights compared to kidney-alone recipients, at a mean follow-up of 5.5 years, all 45 children were reported healthy and developing well (5).

In a case from this year, a P/K recipient reported a second post-transplant pregnancy. Her first pregnancy occurred 1.3 years after a P/K transplant while on tacrolimus, prednisone and azathioprine (switched from MMF to azathioprine pre-conception). Her serum creatinine was 1.3 mg/dL pre- and 1.6 mg/dL after pregnancy. At 30 wks, an 811 gm infant was delivered with multiple

complications of prematurity but was healthy and developing well at 2 years old. Postpartum she resumed tacrolimus and MMF in addition to prednisone. In preparation for a second pregnancy the recipient was changed from tacrolimus and MMF to Gengraf® and azathioprine. Her prepregnancy serum creatinine was 1.5 mg/dL with an increase postpartum to 4.1 mg/dL, at last contact. At 37 wks she delivered a healthy 2,486 gm infant. Postpartum she again resumed tacrolimus and MMF in addition to prednisone.

There were 6 graft losses within 2 years postpartum among the pancreas-kidney recipients. Three recipients lost kidney function (2 retransplanted, one dialysis), one lost pancreas function (insulin), and 2 recipients lost both pancreas and kidney function (one re-transplanted, both subsequently died). Adequate graft function was reported by 26 of 37 (70%) of recipients, with a mean follow-up of 8.4 years since the pregnancy. Of the remaining 11 P/K recipients, 3 died and 8 had varying degrees of graft function.

The impact of pregnancy on graft survival in P/K recipients as well as factors associated with decreased birthweights and gestational ages of their liveborn require further study.

### Female Heart, Heart-Lung, and Lung Recipients

Table 8 details the 33 female heart recipients with 54 pregnancies and 37 livebirths. As previously reported there were no maternal graft losses within 2 years of pregnancy in the female heart recipients reported to the NTPR (6). In some cases, rejection episodes during pregnancy were low grade and additional treatment was not required. One recent entry to the registry is from a recipient maintained on MMF and tacrolimus, who had a spontaneous abortion at 3 weeks. At last follow-up, 24 recipients reported adequate graft function and 2 recipients reported poor or reduced function. There were 7 maternal deaths reported.

Three heart-lung recipients have reported 3 livebirths after transplantation with no new reports this past year to the NTPR. One recipient died 4 years postpartum, which was 12 years after her transplant.

Included in Table 8 are 14 female lung recipients who reported 15 pregnancies (one new pregnancy in the last year). There were 8 (53%) livebirths, 5 (33%) therapeutic abortions and 2 (13%) spontaneous abortions. The mean transplant-to-conception interval was 3.1±2.5

**Table 7. Pregnancy outcomes in 38 female pancreas-kidney recipients with 56 pregnancies reported to the NTPR.**

<b>Maternal Factors</b>	
Transplant to conception interval	3.7 yrs
Hypertension during pregnancy	75%
Diabetes during pregnancy	2%
Infection during pregnancy	55%
Rejection episode during pregnancy	6%
Pre-eclampsia	34%
Graft loss within 2 yrs of delivery	16%
<b>Outcomes (n)<sup>1</sup></b>	<b>(58)</b>
Therapeutic abortions	5%
Spontaneous abortion	14%
Ectopic	2%
Stillbirth	0%
Livebirths	79%
<b>Livebirths (n)</b>	<b>(46)</b>
Mean gestational age	34 wks
Premature (<37 wks)	78%
Mean birthweight	2,096 gms
Low birthweight (<2,500 gms)	63%
Cesarean section	57%
Newborn complications	57%
Neonatal deaths <sup>2</sup> n (%)	
(within 30 days of birth)	1 (2%)
<b>Immunosuppression by pregnancy</b>	<b>n (%)</b>
CsA, aza and prednisone	19 (34)
CsA and prednisone	6 (11)
Neoral®, aza and prednisone	13 (23)
Neoral® and prednisone	3 (5)
Tacrolimus, aza and prednisone	5 (9)
Tacrolimus and aza	2 (4)
Tacrolimus and prednisone	4 (7)
Tacrolimus and sirolimus	1 (2)
Tacrolimus	1 (2)
Gengraf®, aza and prednisone	2 (4)

<sup>1</sup> includes twins; <sup>2</sup> one neonatal death due to sepsis (26 wks, 624 gms)

years. Maintenance immunosuppression during pregnancy was cyclosporine based in 9 (Sandimmune® 7, Neoral® 2) and tacrolimus based in 6. Maternal comorbid conditions during pregnancy included: hypertension 8/15 (53%), rejection 4/15 (27%), diabetes 4/15 (27%), infections 3/15 (20%) and pre-eclampsia 1/8 (13%). Of the 8 liveborn, 3 (38%) were delivered by cesarean section. Mean gestational age was 35±3.8 weeks; 5 (63%)

*Table 8. Pregnancy outcomes in 33 female heart and 14 female lung transplant recipients reported to the NTPR.*

Organ (n)	Heart (33)	Lung (14)
<b>Maternal Factors</b>		
Transplant to conception interval	4.1 yrs	3.1 yrs
Hypertension during pregnancy	46%	53%
Diabetes during pregnancy	4%	27%
Infection during pregnancy	11%	20%
Rejection episode during pregnancy	21%	27%
Pre-eclampsia	10%	13%
Graft loss within 2 yrs of delivery	0%	21%
<b>Outcomes (n)</b>	<b>(54)</b>	<b>(15)</b>
Therapeutic abortions	9%	33%
Spontaneous abortions	17%	13%
Ectopic	2%	0%
Stillbirth	2%	0%
Livebirths	69%	53%
<b>Livebirths (n)</b>	<b>(37)</b>	<b>(8)</b>
Mean gestational age	37 wks	35 wks
Premature (<37 wks)	32%	63%
Mean birthweight	2,717 gms	2,285 gms
Low birthweight (<2,500 gms)	32%	63%
Cesarean section	30%	38%
Newborn complications	22%	75%
Neonatal deaths (within 30 days of birth)	0%	0%
<b>Immunosuppression by pregnancy</b>	<b>n (%)</b>	<b>n (%)</b>
CsA, aza and prednisone	32 (59)	6 (40)
CsA and prednisone	7 (13)	1 (7)
CsA and aza	2 (4)	-
Neoral <sup>®</sup> , aza and prednisone	5 (9)	2 (13)
Neoral <sup>®</sup> and prednisone	1 (2)	-
Neoral <sup>®</sup> and aza	1 (2)	-
Tacrolimus, aza and prednisone	1 (2)	4 (27)
Tacrolimus and prednisone	2 (4)	1 (7)
Tacrolimus alone	2 (4)	1 (7)
Tacrolimus, MMF and prednisone	1 (2)	-

were premature (<37 weeks). The mean birthweight was 2,285±684 grams and 5 infants (63%) were low birthweight (<2,500 grams). There were 6 infants with neonatal complications; there were no neonatal deaths. At last follow-up, the children were reported healthy and developing well including one child who recently had a pacemaker placed due to an arrhythmia at approximately 3.5 years old. Current maternal graft function was reported as adequate in 9 recipients. Five maternal deaths had been reported.

Successful pregnancy outcomes are possible for female lung transplant recipients. Compared to pregnancy outcomes in other solid-organ recipients, female lung recipients had a higher risk of premature delivery, correspondingly lower birthweights, a high risk of rejection during pregnancy, and may have a higher long-term mortality. Whether long-term maternal survival is impacted by pregnancy requires further study. Additional entries would be beneficial to form definitive conclusions for this group of recipients who appear to be especially

*Table 9. FDA pregnancy categories for commonly used immunosuppressive drugs in transplantation.*

Drug	Animal Reproductive Data	Pregnancy Category <sup>1</sup>
Corticosteroids (prednisone, methylprednisolone, others)	Y	B
Azathioprine (Imuran <sup>®</sup> )	Y	D
Cyclosporine (Sandimmune <sup>®</sup> , Neoral <sup>®</sup> , others)	Y	C
Tacrolimus, FK506 (Prograf <sup>®</sup> )	Y	C
Antithymocyte globulin (Atgam <sup>®</sup> , ATG, Thymoglobulin <sup>®</sup> )	N	C
Orthoclone (OKT3 <sup>®</sup> )	N	C
Mycophenolate mofetil (CellCept <sup>®</sup> )	Y	C
Mycophenolic acid (MPA, Myfortic <sup>®</sup> )	Y	C
Basiliximab (Simulect <sup>®</sup> )	Y	B
Daclizumab (Zenapax <sup>®</sup> )	N	C
Sirolimus (Rapamune <sup>®</sup> )	Y	C

<sup>1</sup> FDA categories briefly defined: B = no fetal risk, no controlled studies; C = fetal risk cannot be ruled out; D = evidence of fetal risk

high risk when compared to the other solid organ recipients.

### **Breastfeeding**

Breastfeeding for female transplant recipient mothers remains an area where recommendations are evolving. The NTPR has received reports from women who chose to breastfeed. There were 8 kidney recipients who breastfed their 10 children while on Sandimmune<sup>®</sup> from a few days to 8 months with no new cases reported in the past year. One recipient stopped breastfeeding when an analysis of breast milk revealed detectable Sandimmune<sup>®</sup>. There were 9 kidney recipients (2 new cases) who reported breastfeeding their 10 children while on Neoral<sup>®</sup> for one week up to 2 years. There were 5 kidney recipients who breastfed their 5 children from one week to one year while on tacrolimus. There was one kidney recipient on Gengraf<sup>®</sup> who breastfed her infant for 17 months. In the liver group, there were 7 women who breastfed their 8 infants (3 on Sandimmune<sup>®</sup>, 4 on Neoral<sup>®</sup> and one on tacrolimus). As noted in the liver-kidney section, one recipient continues to breastfeed her infant at 4 months of age while on a tacrolimus-based regimen. There was one pancreas-kidney recipient who breastfed her 2 children for 2 years with no reported problems. One of these cases was previously published (7). There was one lung recipient who reported breastfeeding her infant for 3 months. No heart recipients have reported breastfeeding their infants. At last follow-up there

were no reports of problems in children who had been breastfed.

Thus, while any immunosuppressive drug exposure to the infant could potentially exceed the threshold for safety, the lack of known adverse effects together with the documented benefits of breastfeeding may outweigh the theoretical risks of this exposure (8). Continued study in this area is warranted.

### **FDA Categories**

The FDA categories of agents are summarized in Table 9. No entries to the registry have been reported with exposure to Simulect<sup>®</sup> or Zenapax<sup>®</sup> during pregnancy.

### **Literature Review**

This year there have been general review articles, case reports and single-center data that have contributed to the literature in pregnancy after transplantation. There were 6 general review articles published highlighting pregnancy after transplantation (9-14). A review of the teratogenicity data for current immunosuppression also appeared (15).

Eleven articles were written from outside the US regarding kidney transplant recipients. In a case study reported by Le Ray, et al from France (16), a female kidney transplant recipient conceived while on MMF, tacrolimus, and prednisone. At 18 weeks the pregnancy was discovered and MMF was discontinued and azathio-

prine started. On ultrasound at 22 weeks multiple malformations were noted, and the pregnancy was electively terminated. At autopsy malformations included: cleft lip and palate, micrognathia, ocular hypertelorism, microtia, external auditory duct atresia, and complete agenesis of the corpus callosum. The European Best Practice Group guidelines from 2002 (17) regarding MMF recommend withdrawal at least 6 weeks before a planned pregnancy.

Al Khader, et al from Saudi Arabia (18), reported 35 women with 54 pregnancies (3 women accounted for 22 of the pregnancies) after kidney transplant. Although there were premature livebirths, intra uterine growth retardation and low birthweights, overall neonatal survival was good and there were no structural malformations reported in the liveborn who are now at a mean age of 4.4 years of age. The authors suggested that recipients who have ongoing rejection, uncontrolled hypertension, over 2 grams of urinary protein per 24 hours, or a creatinine above 160 $\mu$ mole/L (1.81mg/dL) should be counseled against pregnancy.

A report from Turkey (19) noted 8 renal recipients on cyclosporine, prednisone and azathioprine with 8 pregnancies.

A paper from Brazil (20) reported on 41 recipients with 44 pregnancies, the majority on cyclosporine-based regimens. Outcomes included: 22% therapeutic abortion, 14% spontaneous abortion, 3% stillborn, and 61% liveborn. There was one maternal death related to eclampsia in a woman without risk factors prior to pregnancy. Preconception, mean serum creatinine was  $1.3 \pm 0.5$ , but 6 months after delivery was  $2.0 \pm 1.8$  ( $p < 0.001$ ). There was no difference in patient or graft survival at one, 5, or 10 years between recipients with and without pregnancy.

From a single Spanish center (21) over a 20-year period, 29 (6.1%) of 476 female kidney transplant recipients became pregnant at least once, for a total of 40 pregnancies. Renal function was stable in 21 (72%), deteriorated postpartum in 8 (28%), and 5 of 8 progressed to dialysis 1-60 months postpartum. There were 28 healthy livebirths, with a mean gestational age of  $33 \pm 4$  wks. There were 9 abortions and 3 stillbirths, for a fetal loss rate of 32%.

In an interesting article from the United Kingdom (22), data were reported on intra-pregnancy renal function for 20 female renal recipients split into 2 groups by the gender of their donor. The authors concluded that there is no clinically significant difference between the gestational

responses of renal allografts based on the donor's gender.

Another UK transplant center (23) reported on 48 pregnancies in 24 kidney recipients. There were 68% live births, 12.5% therapeutic abortions (one for anencephaly), 12.5% spontaneous abortions, 4% intrauterine demise and 2 ectopic (4%). The mean transplant-to-conception interval was 6.5 yrs. Four pregnancies with a transplant-to-conception interval of less than 2 years had poor outcomes: one ectopic, one spontaneous abortion, one stillbirth, and one significantly premature livebirth at 32 weeks with related complications. Interestingly, an association was noted between beta blockers for hypertension (atenolol and metoprolol) and low birth weight, especially with concomitant use of a calcineurin inhibitor. Serum creatinine of  $>1.75$ mg/dL was associated with an increased risk of deterioration of graft function or graft loss.

An article from Spain (24) reported on 3 successful pregnancies in kidney transplant recipients with hepatitis C (HCV). Two of the recipients were PCR+, one was anti-HCV positive but PCR negative. All 3 children were HCV negative at 6 months of age by anti-HCV ELISA2.

An article from Iran (25) looked at the fertility rate in female kidney transplant recipients. There were 126 female transplant recipients age 15-68 yrs, 33 single and 93 married. Normal menses occurred for 55 patients (49.5%). Six of 58 women desiring pregnancy were unable to conceive (infertility = 10.4%). Of 33 pregnancies reported, 16 were unintended (48.5%). Of the 16 unintended pregnancies, 3 had termination, 6 had spontaneous abortion or intrauterine fetal demise, and only 7 had a live birth (44%). This emphasizes the need for counseling women early, before or at the time of transplant about return of fertility, recommended timing of pregnancy, and effective means of birth control.

Another article from Iran (26) studied 10 years of data on menstrual characteristics and pregnancies from 50 female kidney recipients of childbearing age (and 100 healthy women matched for age and parity). Menstrual characteristics improved after transplantation. Eighteen of 33 married women conceived, with a mean transplant-to-conception interval of 35.5 months; 13 of 20 pregnancies had an interval less than 2 years. There were 85% livebirths and 2 neonatal deaths were associated with prematurity. Patients with a transplant-to-conception interval less than 2 years had a higher incidence of hypertension and pre-eclampsia (84% vs. 28%). The

authors concluded the incidence of pregnancy complications was higher if the transplant-to-conception interval is shorter than 2 years.

A study from Poland (27) looked at 33 kidney recipients compared to 31 healthy women in the third trimester of pregnancy. All of the recipients were on prednisone and azathioprine and most were on cyclosporine. The transplant recipients had poorer renal function and higher lipid levels than the controls. After comparing recipients based on immunosuppressive regimen and dose, the hyperlipidemia was ascribed to the immunosuppressive agents (rather than to the decreased level of renal function) and the higher level of proteinuria in the recipients.

A group from Italy (28) collected data on 10 pregnancies in 7 heart recipients between 1991-2002 (dates of pregnancies). There were 2 spontaneous abortions and 8 livebirths. The mean transplant to conception interval was 7 years. All were on cyclosporine-based immunosuppression. Two infants were preterm (25%). The children were reported as developing well at 6 months to 11 years follow-up.

A group from Australia (29) reported experience with 6 pregnancies from 3 liver recipients. Two mothers developed intrahepatic cholestasis of pregnancy during 3 pregnancies. There was one spontaneous abortion and 5 were liveborn.

There were 3 case reports in the literature (30-32). From the UK, a woman with a poorly functioning renal allograft and anti-cardiolipin antibody who was dialysis-independent conceived 18 months following her transplant. She was electively maintained on hemodialysis during the pregnancy and delivered a live infant at 31 weeks gestation. Her renal function returned to prepregnancy levels postpartum and dialysis was stopped (30). Two case reports on heart transplant recipients appeared, one from Italy and the other from New Zealand (31-32).

Danesi, et al (15) authored a concise review of teratogenicity data for current immunosuppressives, with a brief discussion of lactation and the relatively small dose

of drugs delivered to the infant. Weber, et al (33) published an extensive review of vaccinations in immunocompromised patients.

A group of investigators from France (34), studying cyclosporine effects on kidney development in an experimental rabbit model, suggested that potential effects may not be apparent in the newborn and may not manifest until adulthood. Therefore, continued long-term follow-up is warranted.

A group of investigators in the US (35) has established a study analyzing the effects of in-utero exposure on the next generation and has set up a website for accessing this study.

The varying reports in the literature underscore the continued need for reporting to registries and for the publication of center data and case reports.

The guidelines for counseling recipients that were initially proposed in 1976 (36) for the most part remain applicable. Recipients should be in general good health and graft function should be stable and ideally rejection free. Comorbid conditions should be well controlled, especially hypertension and diabetes. While these counseling guidelines were formulated for kidney recipients, they may be extrapolated for other organ recipients as well.

### **Male Recipients**

Pregnancies fathered by the male kidney recipients on newer immunosuppressive medications (Neoral<sup>®</sup>, tacrolimus, MMF and/or sirolimus) were analyzed. There were 97 kidney recipients who fathered 120 pregnancies with 126 outcomes (including twins and triplets). The mean gestational age of the newborns was 39±2.4 weeks and the mean birthweight was 3,244±649 grams (37). The outcomes of pregnancies fathered by male transplant recipients appear similar to those of the general population.

## SUMMARY

The NTPR maintains an ongoing active database to study the safety of pregnancy in transplant recipients and currently includes the outcomes of more than 900 female recipients who became pregnant after their transplant and just over 700 male recipients who fathered one or more pregnancies after receiving a transplant. Analyses include the long-term follow-up of the recipient's graft status and their offspring.

Successful pregnancy outcomes have been noted for each solid organ recipient group. The Registry includes information on 1,097 pregnancies in 716 kidney recipients, 187 pregnancies in 111 liver recipients, 56 pregnancies in 38 P/K recipients and smaller numbers for other organs and combinations of organs. There are periodic reports of recipients with graft dysfunction, rejection, or graft loss that may be related to pregnancy events, though the majority of outcomes reported to the NTPR appear favorable for parent and newborn. Organ-specific issues and comorbidities must also be considered in analyzing outcomes.

The pregnancy issues that face recipients and caretakers with the current newer adjunctive therapies and newer immunosuppressive regimens require ongoing study. The potential risk of teratogenicity must be weighed against the potential risk of rejection when altering drug regimens before planned conceptions or in making dosage adjustments during pregnancy. Unplanned pregnancies present obvious concerns. Pregnancy safety has not been established for either MMF or sirolimus and all centers are encouraged to report pregnancies with exposures to these agents to the NTPR.

Continuing analyses are directed at potential effects of the newer immunosuppressive regimens, not only to identify any risks to the pregnancy from immediate exposure, but also for potential postpartum exposures such as from breastfeeding. As the registry study design allows for continued contact, efforts continue to accrue long-term follow-up of both parent and child.

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