DRUG SAFETY CONCEPTS

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Drug Safety Issues in Pregnancy Following Transplantation and Immunosuppression

Effects and Outcomes

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Contents

Abstract

Successful pregnancy outcomes are possible after solid organ transplantation. While there are risks to mother and fetus, there has not been an increased incidence of malformations noted in the newborn of the transplant recipient. It is essential that there is closely coordinated care that involves the transplant team and an obstetrician in order to obtain a favourable outcome.

Current data from the literature, as well as from reports from the National Transplantation Pregnancy Registry (NTPR), support the concept that immunosuppression be maintained at appropriate levels during pregnancy. At present, most immunosuppressive maintenance regimens include combination therapy, usually cyclosporin or tacrolimus based. Most female transplant recipients will be receiving maintenance therapy prior to and during pregnancy. For some agents, including monoclonal antibodies and mycophenolate mofetil, there is either no animal reproductive information or there are concerns about reproductive safety.

The optimal (lowest risk) transplant recipient can be defined by pre-conception criteria which include good transplant graft function, no evidence of rejection,

minimum 1 to 2 years post-transplant and no or well controlled hypertension. For these women pregnancy generally proceeds without significant adverse effects on mother and child.

It is of note that the epidemiological data available to date on azathioprine-based regimens are favourable in the setting of a category D agent (i.e. one that can cause fetal harm). Thus, there is still much to learn regarding potential toxicities of immunosuppressive agents. The effect of improved immunosuppressive regimens which use newer or more potent (and potentially more toxic) agents will require further study.

The first pregnancy after transplantation occurred in 1958 in a female recipient who had received a kidney from her identical twin. Although not reported until much later,[1] that pregnancy heralded the start of interdisciplinary cooperation that has now dealt with over 7000 pregnancies worldwide in renal transplant recipients alone. In addition, pregnancies are now being reported in liver, pancreas-kidney, heart, heart-lung and lung transplant recipients. Throughout this time, modifications in immunosuppressive regimens have occurred and to date, no specific gross structural malformation patterns have been apparent in the offspring of transplant recipients. This is despite the potential effects of immunosuppressive drug therapy, as well as the occurrence of comorbid factors such as hypertension, diabetes mellitus and renal insufficiency, plus other medications – all of which could theoretically have untoward effects on the developing embryo and fetus.

The publication of case reports and single centre experiences has been useful, but registry data are crucial. Information is being derived from the National Transplantation Pregnancy Registry (NTPR) which was established at Thomas Jefferson University, Philadelphia, US, in 1991 to study the outcomes of pregnancy in female transplant recipients, as well as pregnancies fathered by male transplant recipients.

This article focuses on the pharmacology, adverse effects and potential teratogenicity of the various immunosuppressive medications as well as their effects on perinatal outcome generally. From this point of view it is important to remember the policy of the US Food and Drug Administration (FDA) is to categorise the potential fetal risks of drugs. They do so according to the model: A = controlled studies, no risk; B = no evidence of risk in humans; C = risk cannot be ruled out; D = positive evidence of risk; X = contraindicated. Because of the lack of data, many agents are classified as C. This does not mean that such drugs are safe, but indicates that unknown adverse effects may be present.

Pregnancy outcomes of women who are graft recipients in association with the combinations of immunosuppressive medications are shown in table I. Against this background of NTPR information, coupled with other published studies, we attempt to answer questions regarding management of immunosuppressive regimens when pregnancy follows transplantation.

1. Immunosuppressive Regimens

There are 3 types of immunosuppressive regimens: (i) induction regimens are used during the first weeks post-transplant and employ an antilymphocyte serum in combination with other agents; (ii) antirejection regimens that are high dosage, short term treatments, employing corticosteroids (usually methylprednisolone) and/or an antilymphocyte serum, depending on the severity of the rejection, i.e. corticosteroids in mild rejection and antilymphocyte sera for moderate to severe rejection episodes; and (iii) maintenance regimens which provide long term immunosuppression in order to prevent rejection. These may be initiated from the time of transplant or after an induction

Table I. National Transplantation Pregnancy Registry (NTPR): pregnancies in female transplant recipients

Immunosuppressive regimen	No. of transplant recipients[a]	No. of pregnancies	No. of live births (%)	Mean birth weight (g)	Mean gestational age (wks)	No. of miscarriages (%)	No. of still births (%)	No. of ectopic pregnancies (%)	No. of therapeutic abortions (%)
Kidney transplantation	484	761	599 (78.7)	2580.1	36.1	85 (11.2)	20 (2.6)	6 (0.8)	49 (6.4)
All C regimens	268	407	306 (75.6)	2463.4	35.9	53 (13.1)	10 (2.5)	2 (0.5)	34 (8.4)
C + A + P	192	290	218 (75.2)	2498.5	36	29 (10)	8 (2.8)	1 (0.3)	27 (9.3)
C + P	75	106	73 (69.5)	2300.7	35.5	23 (21.9)	1 (1)	1 (1)	7 (6.7)
C + A	5	9	7 (77.8)	2814	35.2	1 (11.1)	1 (11.1)	0	0
C alone	2	2	2 (100)	2254	33.5	0	0	0	0
All CM regimens	8	8	6 (75)	2480.6	36.3	2 (25)	0	0	0
CM + A + P	5	5	4 (80)	2416.8	35.8	1 (20)	0	0	0
CM + P	2	2	1 (50)	2920	38	1 (50)	0	0	0
CM alone	1	1	1 (100)	2296.3	37	0	0	0	0
All C then CM regimens	5	5	4 (80)	2335.3	37	0	1 (20)	0	0
C then CM + A + P	3	3	2 (66.7)	2693.2	39	0	1 (33.3)	0	0
C then CM + P	2	2	2 (100)	1977.4	35	0	0	0	0
All T regimens	8	8	6 (75)	2216.1	32.7	2 (25)	0	0	0
T + A + P	3	3	2 (66.7)	2168.7	32.5	1 (33.3)	0	0	0
T + MM + P	1	1	1 (100)	2240	32	0	0	0	0
T + P	2	2	2 (100)	2707.4	35.5	0	0	0	0
T alone	2	2	1 (50)	1304.1	28	1 (50)	0	0	0
All non-C regimens	195	331	275 (83.1)	2722.5	36.4	28 (8.5)	9 (2.7)	4 (1.2)	15 (4.5)
A + P	172	294	241 (82)	2698.5	36.4	25 (8.5)	9 (3.1)	4 (1.4)	15 (5.1)
P alone	18	30	27 (90)	2935.8	35.7	3 (10)	0	0	0
A alone	4	7	7 (100)	2717.2	37.8	0	0	0	0
No immunosuppression	2	2	2 (100)	2749.9	37	0	0	0	0
Liver transplantation	60	95	71 (74.7)	2696.3	36.8	14 (14.7)	2 (2.1)	0	8 (8.4)
All C regimens	49	79	59 (74.7)	2641.3	36.7	10 (12.7)	2 (2.5)	0	8 (10.1)
C + A + P	29	47	35 (74.5)	2542.4	36.7	5 (10.6)	2 (4.3)	0	5 (10.6)
C + P	20	29	21 (72.4)	2687.1	36.5	5 (17.2)	0	0	3 (10.3)
C + A	1	1	1 (100)	4097	36	0	0	0	0
C alone	1	2	2 (100)	3161	37.5	0	0	0	0
All T regimens	8	11	8 (72.7)	2955.8	36.9	3 (27.3)	0	0	0
T + A + P	3	4	2 (50)	3075.9	38.3	2 (50)	0	0	0
T + P	3	3	2 (66.7)	2992.3	39.2	1 (33.3)	0	0	0
T alone	3	4	4 (100)	2877.5	35.1	0	0	0	0

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Table I. Contd

Immunosuppressive regimen	No. of transplant recipients[a]	No. of pregnancies	No. of live births (%)	Mean birth weight (g)	Mean gestational age (wks)	No. of miscarriages (%)	No. of still births (%)	No. of ectopic pregnancies (%)	No. of therapeutic abortions (%)
No immunosuppression	2	4	3 (75)	2835	38	1 (25)	0	0	0
Pancreas-kidney transplantation	14	19	16 (84.2)	1994.4	35	2 (10.5)	0	0	0
All C regimens	12	17	14 (82.4)	1985.3	35	2 (11.8)	0	0	1 (5.9)
C + A + P	8	13	10 (76.9)	1849.5	35	2 (15.4)	0	0	1 (7.7)
C + P	4	4	4 (100)	2324.8	34.9	0	0	0	0
All CM regimens	2	2	2 (100)	2058	35.5	0	0	0	0
CM + A + P	2	2	2 (100)	2058	35.5	0	0	0	0
Heart transplantation	19	35	22 (62.9)	2685.3	36.4	7 (20)	0	1 (2.9)	5 (14.3)
All C regimens	17	32	21 (65.6)	2659.3	36.5	6 (18.8)	0	1 (3.1)	4 (12.5)
C + A + P	16	28	18 (64.3)	2593.8	36	5 (17.9)	0	1 (3.6)	4 (14.3)
C + P	1	4	3 (75)	3052.3	39.3	1 (25)	0	0	0
All T regimens	2	2	1 (50)	3232	36	1 (50)	0	0	0
T + A + P	2	2	1 (50)	3232	36	1 (50)	0	0	0
P + A	1	1	0			0	0	0	1 (100)
Heart-lung transplantation	2	2	2 (100)	2537.5	36.8	0	0	0	0
All C regimens	2	2	2 (100)	2537.5	36.8	0	0	0	0
C + A + P	2	2	2 (100)	2537.5	36.8	0	0	0	0
Lung transplantation	7	7	4 (57.1)	1920.8	32.1	3 (42.9)	0	0	0
All C regimens	6	6	3 (50)	2022.3	32.8	3 (50)	0	0	0
C + A + P	5	5	2 (40)	1701	33.5	3 (50)	0	0	0
C + P	1	1	1 (100)	2665	31.5	0	0	0	0
T alone	1	1	1 (100)	1616	30	0	0	0	0
Liver-kidney transplantation	2	2	2 (100)	2994	38.5	0	0	0	0
All C regimens	2	2	2 (100)	2994	38.5	0	0	0	0
C + A + P	1	1	1 (100)	2665	39	0	0	0	0
C + P	1	1	1 (100)	3323	38	0	0	0	0
All transplantations	**588**	**921**							

a Some patients received more than 1 immunosuppressive regimen for different pregnancies.

A = azathioprine; **C** = cyclosporin; **CM** = cyclosporin microemulsion (Neoral®); **MM** = mycophenolate mofetil; **non-C** = no cyclosporin or tacrolimus; **P** = prednisone; **T** = tacrolimus.

regimen. Maintenance drug dosages are usually tapered over the first post-transplant year to a baseline level which continues indefinitely. Most recipients who become pregnant do so 2 or more years after transplantation, when they are most likely to be receiving a maintenance regimen.

1.1 Commonly Used Immunosuppressive Agents

These are summarised in table II.

1.1.1 Corticosteroids

Corticosteroids have broad immunosuppressive effects, inhibiting all types of leucocytes. Complications associated with their use include diabetes mellitus, aseptic necrosis, peptic ulcer disease and psychiatric disturbances. Methylprednisolone is used intravenously for induction or treatment of rejection, and prednisone or prednisolone is used orally in maintenance therapy. Corticosteroids have been part of virtually all immunosuppressive regimens, invariably combined with other agents.

Prednisone is biologically inert and is converted in the liver to prednisolone, the biologically active compound. Blood concentrations are not measured as bioavailability is high. Although it is generally considered that therapeutic dosages of prednisone and prednisolone have low teratogenic risks, the data are insufficient to say that there is no risk.[2] Of interest, the issue of teratogenicity dates back to studies of pregnant mice treated with cortisone which caused cleft palate in the offspring.[3] A literature survey, however, has revealed 468 cortisone-exposed gravidas in whom the fetal malformation rate was 3.5%, which was judged to be no greater than the general population.[4] In this survey, pregnancies were excluded if other potentially teratogenic agents such as azathioprine were used. Another study compared the offspring of women (n = 19) who received prednisone 10 mg/day for treatment of infertility (continued throughout pregnancy), with 67 offspring from women who had not received prednisone. An analysis of variance revealed that offspring exposed prenatally to prednisone weighed significantly less than control offspring.[5] Methylprednisolone, prednisolone and prednisone are classified as category B drugs.

1.1.2 Azathioprine

Following absorption, azathioprine, an inhibitor of purine metabolism, is rapidly converted in the liver into a number of metabolites including its active metabolite mercaptopurine, which has been found in cord blood.[6] The introduction of azathioprine in combination with prednisone in 1962 opened the door to clinical kidney allograft (genetically nonidentical) transplantation, and it is still used in many transplant protocols despite the potential for leucopenia. It was suggested in 1 report that the embryo may be protected against the effects of azathioprine in early pregnancy if it lacks

Table II. Immunosuppressive drugs commonly used in transplantation

Drug	Dosage range (mg/kg/day)	Animal reproductive data?	Published pregnancy clinical outcomes?	FDA pregnancy category
Corticosteroids				
prednisone, prednisolone	5-20 mg/day	Yes	Yes[a]	B
methylprednisolone	500-1000 mg/day (antirejection)	Yes	Yes[a]	B
Azathioprine	0.5-1.5	Yes	Yes[a]	D
Cyclosporin	3-10	Yes	Yes[a]	C
Tacrolimus	0.05-0.2	Yes	Yes[a]	C
Mycophenolate mofetil	2-3 g/day	Yes	No[a]	C
Muromonab CD3 (OKT3)	2.5-10 mg/day	No	Yes[a,b]	C
Antithymocyte globulin	15-30	No	Yes[b]	C

a Registry data.

b Case reports only.

B = no evidence of risk in humans; **C** = risk cannot be ruled out; **D** = positive evidence of risk; **FDA** = US Food and Drug Administration.

the enzyme inosinate pyrophosphorylase, which is involved in the conversion of mercaptopurine to the components that act on DNA and dividing cells.[7] When more potent and more specific immunosuppressants became available, the role of azathioprine changed from that of a primary drug (prednisone plus azathioprine at dosages of 1.5 to 3 mg/kg/day) to an adjunctive drug (prednisone plus cyclosporin or tacrolimus plus azathioprine at dosages of 0.5 to 1.5 mg/kg/day).

Azathioprine is a category D agent. It has demonstrated teratogenicity in animal studies, with high incidences of embryonic resorption and/or fetal anomalies. Of interest is the fact that fertility problems affect the female offspring of mice, where the mother had been given low dosages of mercaptopurine. This underscores the need for long term follow-up of the children of women received azathioprine following transplantation.[8]

Congenital anomalies have been noted among offspring of rabbits where dosages of azathioprine from 5 to 15 mg/kg/day were used.[9]

Fortunately, clinical data so far indicate that the teratogenic risk to a child born after *in utero* exposure to azathioprine is small.[2] In one series, however, where birth anomalies were present in 7 out of 103 offspring, the mothers of affected babies had been taking a significantly higher daily dosage of azathioprine compared with those who had normal babies (2.64 *vs* 2.02 mg/kg/day).[10] As this analysis was based on a relatively small number of babies with birth anomalies, it could still be due to chance.

From a review of pregnancy outcomes in the azathioprine era, certain neonatal problems are apparent: thymic atrophy, leucopenia, anaemia, thrombocytopenia, chromosome aberrations, reduced immunoglobulin levels, infections and septicaemia, as well as sequelae from pre-term delivery and intrauterine growth retardation.[11-13] It has been suggested that adjustment of azathioprine dosage to maintain maternal leucocyte counts within normal physiological limits for pregnancy could avoid neonatal leucopenia and thrombocytopenia.[14] In a case report, the offspring of a 26-year-old renal transplant recipient maintained on azathioprine and prednisone was noted to have chromosomal damage in peripheral blood lymphocytes, which disappeared months later.[15] Of note was the presence of similar chromosome abnormalities in the mother herself. In another case report, a woman receiving long term azathioprine therapy who had a history of systemic lupus erythematosus delivered an infant born with pre-axial polydactyly.[16]

Even though animal studies and occasional case reports have raised concerns regarding pregnancy exposure to azathioprine, the overall consensus based on several thousand pregnancies is that there is no predominant or specific gross malformation pattern attributable to the drug.[2]

1.1.3 Cyclosporin

Cyclosporin became the mainstay of immunosuppression when it was introduced in the early 1980s. Cyclosporin is a cyclic 11 amino acid peptide and is a category C agent. The initial event for a cellular immune response occurs when a helper T cell encounters the appropriate antigen on the surface of an antigen-presenting cell along with other signals that define self. Cyclosporin blocks the helper T cell's signal transduction mechanism by inhibiting calcineurin, a rate-limiting phosphatase required to activate the promoters needed for transcription of the cytokine genes essential for T cell activation and proliferation. The most prominent of these cytokines is interleukin-2.

Cyclosporin is fat soluble, has variable bioavailability and is monitored by measuring trough concentrations, in contrast to corticosteroids and azathioprine. The usual oral dosage range is from 3 to 10 mg/kg/day. The main toxicities of cyclosporin are nephrotoxicity and hypertension. Other adverse effects include tremor, hirsutism and hyperlipidaemia. Cyclosporin effects only lymphocytes, without depressing bone marrow or leucocyte counts. Therefore, theoretically, it is associated with lower risks of infection and neoplasia than corticosteroids and azathioprine.

Cyclosporin fetotoxicity was evident when female Lewis rats were given 25 mg/kg/day (by gas-

tric intubation) from the time of mating to 20 days post mating, with fetal mortality and cyclosporin-induced proximal renal tubular cell damage noted in fetal kidneys. Abnormalities in fetal kidneys were not found at a dosage of 10 mg/kg/day.[17] In another study, cyclosporin was administered to pregnant mice in relatively high and maternally toxic dosages (30 mg/kg/day, by injection) for limited periods. While lethal embryo toxicity and fetotoxicity were often noted as leading to resorptions, teratogenicity was not demonstrated. Histological examination revealed alterations in maternal thymus, liver, kidney and spleen; however, most of these alterations had disappeared by 1 week following the last injection.[18]

A review of the literature has identified at least 13 children of women treated with cyclosporin who were born with congenital anomalies, but there was no recurring pattern. Thus, given the reasonable quality and quantity of data on which risk estimates have been based, the consensus is that the magnitude of the teratogenic risk for malformations is minimal, with a small to moderate risk for fetal growth retardation.[2]

A new microemulsion formulation of cyclosporin (Neoral®) was approved by the FDA in August 1995 for use in clinical transplantation. This formulation has more reliable absorption characteristics than the original form (decreased intra- and interpatient variability) and has more predictable pharmacokinetics.[19,20]

1.1.4 Tacrolimus

Tacrolimus is a macrolide antibiotic that acts in a similar way to cyclosporin (i.e. it is a calcineurin inhibitor) but it is more potent. The increased potency of tacrolimus is manifest both *in vitro* and in clinical use, i.e. decreased incidence of rejection. The main adverse effects of tacrolimus are nephrotoxicity, hypertension, neurotoxicity and diabetes mellitus.

In a recently published multicentre trial in non-pregnant kidney graft recipients treated with tacrolimus or cyclosporin, the major adverse effect associated with tacrolimus use was diabetes mellitus which occurred in 19.9% of recipients at 12 months; however, the incidence had decreased to 12.6% by 18 months.[21] In contrast, in the cyclosporin-treated group, diabetes mellitus occurred in 4% of recipients at 12 months and 3.3% of recipients at 18 months. There were no differences in the incidences of nephrotoxicity or hypertension between the 2 groups. A potential benefit of the tacrolimus therapy was a decrease in the incidence of hyperlipidaemia.[21] NTPR data for pregnant female renal recipients showed a lower prevalence of hypertension in tacrolimus recipients compared with cyclosporin microemulsion recipients (27 *vs* 61%, respectively) but a higher prevalence of diabetes mellitus (27 *vs* 6%, respectively).

Tacrolimus, like cyclosporin, is a category C drug. The clinical tacrolimus oral dosage range is 0.05 to 0.2 mg/kg/day and drug dosages are adjusted via trough concentrations.

Tacrolimus use in murine pregnancy revealed that high dosages (1.28 mg/kg/day by intramuscular injection) did not have any obvious detrimental effects on maternal health, but caused resorption of all fetuses, whereas in a lower dosage group (0.16 mg/kg/day), the fetuses that survived did not appear to be different from controls. This study concluded that tacrolimus could have adverse effects on pregnancy, but that maternal and fetal toxicities are dose-dependent.[22]

The FDA approved tacrolimus for liver transplantation in 1995 and kidney transplantation in 1997,[23] so reports to the NTPR are increasing. A recent report from a large single centre experience of pregnancy after liver transplantation using tacrolimus showed newborns (n = 25) with gestational ages and birthweights similar to previous reports in liver recipients and no predominant malformation pattern, but there was a 36% incidence of transient perinatal hyperkalaemia and mild reversible renal impairment.[24] Tacrolimus dosages were modestly increased during 5 of the 27 pregnancies in this study and decreased in 6. There was a lower incidence of maternal hypertension and pre-eclampsia compared with previous reports of women receiving other regimens. There were no peripartum graft losses.

1.1.5 Mycophenolate Mofetil

Mycophenolate mofetil is a prodrug that undergoes ester hydrolysis in the intestine and blood to form the active metabolite, mycophenolic acid. This drug is a reversible inhibitor of inosine monophosphate dehydrogenase and inhibits de novo purine synthesis. Lymphocytes are very dependent on *de novo* purine synthesis (as opposed to the salvage pathway) and hence are more susceptible to the antiproliferative effects of mycophenolic acid. The main adverse effects of mycophenolate mofetil are gastrointestinal and leucopenia. In clinical kidney trials, fewer acute rejection episodes and a longer time to first rejection episode were noted when comparing mycophenolate mofetil in combination with cyclosporin and corticosteroids following antithymocyte globulin induction with an identical regimen using azathioprine instead of mycophenolate mofetil.[25] In addition, it may be used to treat ongoing refractory rejection.[26] The oral dosage range in adults is 2 to 3 g/day, which may be titrated against clinical adverse effects, i.e. gastritis, diarrhoea and leucopenia. Blood concentrations are not measured.

Although a category C drug, the package insert notes that animal studies indicate teratogenicity at dosages below those causing maternal toxicity and at dosages within the therapeutic range. There is, therefore, concern about its use in pregnancy. Epidemiological studies are not yet available. Recently, 1 pregnancy with mycophenolate mofetil exposure has been entered in the NTPR database (see table I). Although the baby was born prematurely, no structural malformations were reported. Furthermore, data are still accruing as to the long term benefits of this agent, specifically whether fewer acute rejections do, in fact, result in better long term graft survival. Thus, any risk-benefit discussion involves a decision as to whether continuation of this drug during pregnancy is worth the potential risk to the fetus if there is not a proven benefit with respect to long term graft survival for the mother.

1.1.6 Muromonab CD3 (OKT3)

Muromonab CD3 (OKT3) is a murine monoclonal immunoglobulin (Ig) G_{2a} antibody that binds to the CD3 antigen on human T cells, which is part of the T cell receptor for antigen/activation. When muromonab CD3 binds to the T cell receptor-CD3 complex, it blocks the function of helper T cells. Muromonab CD3 is used in both induction and antirejection regimens.

Animal reproductive studies have not been conducted with muromonab CD3, which is a category C agent, and it is not known whether muromonab CD3 can cause fetal harm when administered to pregnant women. As a murine IgG antibody, it may cross the human placenta. Adverse effects of muromonab CD3 include a first dose reaction which is due to cytokine release, causing fever, chills and bronchospasm. The duration of therapy is usually 10 to 14 days.

1.1.7 Antithymocyte Globulin

Another agent that may be used for 10 to 14 days as induction or antirejection therapy is antithymocyte globulin, a polyclonal antilymphocyte serum harvested from horses or rabbits which depletes T cells. Its main adverse effects are fevers and chills. Antithymocyte globulin is a category C drug. As with muromonab CD3, it has neither been evaluated in pregnant women, nor have animal reproductive studies been conducted.

2. Pregnancy Outcomes

Surveys and literature reviews of pregnancies in the azathioprine era were encouraging for mother and newborn. There was a 40 to 50% incidence of prematurity and an incidence of intrauterine growth retardation of about 20%. No specific or predominant malformation patterns were identified in the newborn.[13]

With azathioprine-based pregnancies as a standard, the introduction of cyclosporin initially caused concern with regard to its safety during pregnancy.[27] The NTPR at Thomas Jefferson University was established in 1991. Data are obtained using a single page questionnaire filled out by the transplant recipient; follow-up data are obtained

from transplant centres and by interviews with transplant recipients and centres. Early on, analysis of data from the NTPR revealed that regardless of the combination of immunosuppressive regimen, i.e. cyclosporin-based or azathioprine-based, the incidence of prematurity was similar.[28] Mean birthweights were lower in the offspring of women receiving cyclosporin when compared with the offspring of women receiving azathioprine and the former group had a greater percentage of low birthweight and very low birthweight infants.

Using a multivariate analysis of female renal transplant recipients comparing cyclosporin-based recipients with azathioprine-based recipients, hypertension and serum creatinine levels ≥1.5 mg/dl were the most significant factors associated with lower birthweight. Moreover, the incidence of drug-treated hypertension prior to pregnancy was greater among the cyclosporin-based recipients (52 *vs* 19%), and hypertension is a well known risk factor for lower birthweight newborns across all gravidas.[29,30] There was no evidence of predominant types of malformations amongst the offspring of either the azathioprine or cyclosporin group.[31]

Studies outside the NTPR have demonstrated the accumulation of cyclosporin in placenta and fetal organs.[32-34] Of interest, it has also been shown that cyclosporin exposure *in utero* does not lead to significant long term nephrotoxic effects in the offspring.[35,36] In a single centre report, peripheral blood lymphocyte populations were analysed from children exposed *in utero* to cyclosporin (n = 7) or to azathioprine (n = 4). Exposure to cyclosporin slightly delays T cell development whereas exposure to azathioprine appeared to slightly accelerate development.[37] Serological testing indicated that immunoglobulin and complement levels, as well as seroconversion in response to vaccination, were normal among the cyclosporin exposed children. Thus, the immune system in humans appears to be resilient and adaptable to the presence of cyclosporin during fetal development.

2.1 Breastfeeding

The question arises as to whether it is safe for women receiving immunosuppressants other than corticosteroids to breastfeed.[38] Immunosuppressive agents are excreted in breastmilk and, while the number of women tested is small, drug concentrations in breastmilk are roughly comparable to maternal blood concentrations.[24,39,40] However, the dosage delivered to the infant via this route is very small,[41] and in 8 infants breastfed by mothers receiving cyclosporin, their blood concentrations were below the assay's sensitivity (i.e. <30 mg/ml).[41,42]

More information is needed about whether such breastmilk drug concentrations are trivial or substantial from a biological point of view, and data are needed for drugs other than cyclosporin. Human breastmilk does confer many benefits for the infant,[43] and advice to the mother should balance the risks from the drug(s) against the undoubted disadvantages of formula feeding. Indeed, despite the current weight of opinion that mothers who are transplant recipients should not breastfeed until more definitive data are available, some mothers will choose to ignore this advice.[39,44]

2.2 Long Term Prognosis of Renal Transplant Patients

Two well designed case-controlled studies have demonstrated that in the presence of stable graft function, pregnancy does not appear to adversely affect graft function.[45,46] One study suggested that a minor deleterious effect of pregnancy on graft function could not be excluded, but no specific adverse factors could be determined.[47] As might be expected, if chronic rejection is present prior to pregnancy, these recipients are at a greater risk of pregnancy-related graft loss.[48]

2.3 Rationale Behind Cyclosporin Dosage in Pregnancy

Prior to the introduction of cyclosporin (for which trough concentrations are used to adjust dosages) titration of immunosuppressive dosages was

empiric. On the one hand, concerns about the potential teratogenicity or nephrotoxicity of cyclosporin during pregnancy have led some to hypothesise that cyclosporin concentrations should be kept as low as possible during pregnancy.[35] Others have suggested that with the increased volume of distribution of pregnancy, altered maternal gut motility, fetal hepatic drug metabolism and the potential for falling drug concentrations, dosages should be increased to maintain an adequate therapeutic concentration.[49,50] In a survey of 32 pregnancy outcomes in heart transplant recipients, most gravidas (59%) were taking triple drug immunosuppression (azathioprine, corticosteroids and cyclosporin). The most common alteration to therapy (41%) involved increasing cyclosporin dosages in response to decreasing blood concentrations.[51] Similar changes were noted in 2 case reports of post–liver transplant recipients during pregnancy.[52,53]

To specifically address this question of cyclosporin dosages during pregnancy, the NTPR defined 2 renal recipient groups for a case-controlled study.[54] A graft dysfunction group (n = 20) was defined as recipients who delivered a live baby from their first post-transplant pregnancy and had complications defined as: graft dysfunction, rejection during pregnancy or within 3 months of delivery, or graft loss during pregnancy or within 2 years of delivery. A stable graft function group (n = 20) was defined as those who delivered a live infant from their first post-transplant pregnancy without any graft complications. Mean birthweights and gestational ages were lower in the offspring of the graft dysfunction group compared with the offspring of the stable graft function group (1949 *vs* 2428g and 33.9 *vs* 36 weeks, respectively). Other significant findings included: (i) recipients in the graft dysfunction group had a higher mean serum creatinine level prior to pregnancy (1.68 *vs* 1.41 mg/dl), whilst their mean daily dosage of cyclosporin was less (3.10 *vs* 4.50 mg/kg/day); and (ii) in both groups, blood cyclosporin concentrations decreased during pregnancy. The lowest mean cyclosporin daily dosage was evident in the third trimester graft dysfunction group (2.49 mg/kg/day).[54]

These results prompted an analysis of dosage practices for the entire cyclosporin renal recipient database (n = 260 pregnancies) as well as the 2 subgroups themselves. Although most recipients (82%) did not report a change in cyclosporin dosage during pregnancy, 37% of the graft dysfunction group had either a decrease (21%) or a discontinuation (16%) of cyclosporin. In this retrospective analysis, however, it cannot be determined whether cyclosporin dosages were decreased because of deteriorating renal graft function, concerns of fetotoxicity, or for other reasons, and/or whether such changes contributed to decline in graft function. Worse graft outcomes were noted when cyclosporin dosages were either decreased or discontinued during pregnancy, strengthening the argument for at least maintenance dosages of cyclosporin during pregnancy.[55]

2.4 Nonrenal Transplant Recipients

Data are accruing for heart,[51,56] heart-lung,[51] lung,[57,58] liver[59,60] and pancreas-kidney transplant recipients.[61] In general, if recipients enter pregnancy with stable graft function, pregnancy appears to be well tolerated and no specific adverse effects seem to be related to the pregnancy. In female liver transplant recipients, those with recurrent hepatitis B or C virus infection or cytomegalovirus infection may be at significant risk for pregnancy-related problems and/or graft loss.[62] Smaller birthweights have been noted among the offspring of pancreas-kidney transplant recipients when compared with the rest of the NTPR database, but in contrast to offspring of kidney-only transplant recipients with diabetes mellitus, newborn complications are fewer.[63] While the early experience is limited (n = 7 cases in the NTPR), female lung transplant recipients may be at a greater risk of pregnancy-related complications when compared with other organ transplant recipients.

Table III. National Transplantation Pregnancy Registry: outcomes of female liver transplant recipients with acute rejection during pregnancy

Recipient no.	Maternal age (y)	Transplant to conception interval (y)	Outcome	Gestational age (wks)	Birthweight (g)	Newborn complications
1	29	2.3	Live birth	35	1673	Jaundice
2	22	0.7	Live birth	30	1417	
3	34	3.2	Live birth	37	2693	
4	20	1.2	Live birth	39	2920	
5	33	1.5	Live birth	38	2892	
6	26	1.3	Live birth	34	2268	
7	34	–0.3[a]	Live birth	27	964	Bronchopulmonary dysplasia
8	24	1.3	Therapeutic abortion			
9	23	3.7	Therapeutic abortion			
10	29	–0.3[a]	Still birth	26		
Mean[b]				34.3[b]	2118[b]	

a Transplanted during pregnancy.
b Mean for live births.

2.5 Transplant Recipients Not Receiving an Immunosuppressive Regimen

In the NTPR, 2 kidney transplant recipients and 2 liver transplant recipients were not receiving an immunosuppressive regimen prior to pregnancy and all 4 gave birth to babies that did not have structural problems. Of the 2 kidney transplant recipients, one received a kidney from her identical twin, and the other had immunosuppression stopped 7 years after transplantation, with pregnancy 3 years later. One of the liver transplant recipients (transplanted for trauma) was maintained on prednisone for only 1 year post-transplant with pregnancy 14 years later. The other women had received a heterotopic liver transplant for fulminant hepatic failure. Her own liver recovered function with 2 successful pregnancies afterwards, at 4.2 and 6 years post-transplantation.

2.6 Newer Immunosuppressive Agents

Data are accruing in the NTPR on the newer immunosuppressive agents. For instance, outcomes of pregnancies in transplant recipients receiving maintenance therapy with tacrolimus-based regimens (one of whom was also receiving mycophenolate mofetil), and cyclosporin microemulsion–based regimens reveal livebirth percentages and mean birthweights similar to previous findings (table I), and no congenital structural malformations have been reported to date.

2.7 Concerns About Rejection

The reason for maintaining adequate immunosuppressive concentrations during pregnancy is to avoid rejection, which has been a complication of 5 to 10% of pregnancies in the NTPR database (although not all cases were biopsy proven). Treatment of acute rejection during pregnancy has generally been to increase the amount of immunosuppression, usually with corticosteroids. The increase in immunosuppressive exposure increases the potential for drug toxicity as well as infections, such as cytomegalovirus. Thus, part of the reason for the recommendation to wait 1 to 2 years post-transplant before pregnancy is because the risk of acute rejection is highest in the first year post-transplant and falls with time after transplantation. Successful pregnancy outcomes for mother and newborn have been reported when rejection episodes have been treated, even when muromonab CD3 was used (tables III and IV).

Particularly complex are situations in which liver transplantation is required during pregnancy. Five cases have been reported in the literature, 2 of

which are in the NTPR database.[62,64-68] One recipient was transplanted for fulminant hepatitis and had a rejection episode treated with methylprednisolone followed by a course of muromonab CD3. A cytomegalovirus infection at the end of the pregnancy was treated with ganciclovir. She delivered a live baby at 27 weeks gestation, who developed bronchopulmonary dysplasia and required long term supplemental oxygen. Both mother and newborn survived.[62] Obviously interdisciplinary care is mandatory in such circumstances and the mother's well-being must be maintained.

2.8 Current Awareness

Concern among practitioners with respect to pregnancy following transplantation focuses not only on the long term maternal prognosis but also on potential adverse effects that medications may have on the developing fetus. This is a reasonable concern in the post-thalidomide era. Adverse pregnancy outcomes resulting from medication exposure may result in the following: (i) embryonic or fetal death; (ii) structural malformation in a liveborn; (iii) growth retardation in a liveborn; and (iv) functional problems in a liveborn. The FDA categories were devised in an effort to provide guidelines for practitioners on fetal risk.

During a recent public hearing (September 12, 1997), the FDA invited comments on the usefulness of these categories. It was pointed out that animal studies have accurately predicted only 2 agents as human teratogens, valproic acid (sodium valproate) and the retinoids. Others have been identified by epidemiological studies. Animal studies do not measure blood concentrations or the effect of the drug combinations that transplant recipients must take. More than 60% of drugs are listed as categories C and D, thus the practitioner is not able to counsel a transplant recipient that there is no risk associated with pregnancy. In contrast to other situations where drug exposure during pregnancy may be unnecessary, immunosuppressive agents are essential for the maintenance of graft function and patient survival, and hence well-being.

It must not be forgotten that there is a background malformation risk of approximately 3% for all gravidas. To date, there is no indication that this incidence has increased in relation to the use of complex medical regimens in many types of patients. Whether more subtle effects will become apparent later in childhood is as yet undetermined, but preliminary NTPR data on long term follow-up of children are encouraging.

3. Conclusion

Transplant recipients should be advised to wait 1 to 2 years after transplant before considering childbearing.[69,70] Those with stable graft function, in the absence of rejection, graft dysfunction or deterioration, should still be apprised of the high risk of prematurity and low birthweight, although maternal risks appear low. Close surveillance throughout pregnancy appears to be warranted, al-

Table IV. National Transplantation Pregnancy Registry: outcomes of pregnancies in patients receiving therapy with muromonab CD3 (OKT3) for rejection

Organ	Transplant to conception interval (y)	Antirejection treatment sequence	Pregnancy outcome	Graft loss[a]
Kidney	0.46	Methylprednisolone, muromonab CD3	Live birth	No
Kidney	2.2	Methylprednisolone, muromonab CD3, tacrolimus	Live birth	Yes
Pancreas-kidney	3.59	Prednisone, muromonab CD3	Therapeutic abortion	Yes
Pancreas-kidney	1.17	Muromonab CD3	Live birth	Yes
Liver	–0.33[b]	Methylprednisolone, muromonab CD3	Live birth	No

a Graft loss within 2 years of delivery.

b Intrapartum liver transplant.

though in most cases, a successful outcome for mother and child can be anticipated. The use of the pregnancy categories should not be the sole reason for choosing a particular drug. Agents such as cyclosporin and tacrolimus would appear to offer some advantage as blood concentrations can be measured. At present, no safety guidelines can be given for mycophenolate mofetil, muromonab CD3 or antithymocyte globulin. Further surveillance of the newer agents is crucial. Prospective pregnancy registry studies may help to better address these issues.

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