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Immunosuppression in Pregnancy
Choices for Infant and Maternal Health

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Contents

Abstract

Successful pregnancy outcomes are possible after all types of solid organ transplantation and thousands of successful pregnancies in such women have been reported. As immunosuppressive medications are required to maintain adequate graft and maternal survival, major concerns are the effect of these agents on the fetus and the effect of pregnancy on the well being of mother and graft, against a background of continuing advances and modifications in immunosuppressive therapy.

Women should avoid unnecessary medications during pregnancy but clinicians worry most about teratogens; agents (environmental, pharmaceuticals or other chemicals) that cause abnormal development, whether this be an overt structural birth defect or more subtle derangements of embryonic or fetal development. A concern is that any agent or combination of agents and maternal condition(s) may be teratogenic, a risk that is increased in the transplant population. The goal of immunosuppression is to ensure graft and patient survival by preventing acute rejection. Combinations of agents allow for synergistic effects while minimising drug toxicities. No specific combination has been deemed op-

timal and the effects of more recently available combinations require further study.

Although there are known theoretical risks to mother and fetus, successful pregnancies are now the rule in transplant recipients. This is without an apparent increase in the type or incidence of malformations in the newborns, and usually with no evidence of graft dysfunction and/or irreversible deterioration either related to prepregnancy graft problems or unpredictable gestational factors.

For immunosuppression, what is best for the mother and her survival should ensure the best outcome for the fetus and, although no specific malformation pattern has been reported to date, there are some interesting trends worthy of continued analyses. A balance of good maternal and graft outcome with the lowest risk of fetal toxicity must be the goal of management.

1. Background

The first known posttransplant pregnancy was in 1958 (but not reported until 1963), in a patient who had received a kidney from her identical twin and delivered a healthy baby boy by caesarean section.[1] In 1976, a detailed case report presented a management scheme for a renal recipient during pregnancy. The recipient took prednisone and azathioprine, had labour induced at 36 weeks, and a healthy baby boy in the twenty-fifth percentile was delivered. No neonatal resuscitation was required and no malformations occurred. The patient maintained stable graft function.[2] This case report emphasised the importance of close follow-up of these patients as well as the need for accepted protocols to aid collation of the experiences of individual institutions, thus contributing to a better understanding of the issues involved with pregnancy in this population. This pregnancy did not appear to have an adverse effect on transplant function and fetal well being, but the question was raised as to whether the pregnancy might have had subtle effects on transplant function or on the newborn.

This case report and a survey of literature at that time derived a set of criteria for counselling female renal transplant recipients contemplating pregnancy which included: (i) good general health for at least 2 years since transplantation; (ii) stature compatible with good obstetric outcome; (iii) no proteinuria; (iv) no significant hypertension; (v) no evidence of renal rejection; (vi) no evidence of pelvicalyceal distention on a recent excretory urogram; (vii) plasma creatinine level of 2 mg/dl (180 mmol/L) or less; and (viii) drug therapy using prednisone ≤15 mg/day and azathioprine ≤3 mg/kg/day.[2]

Beginning in the early 1960s, immunosuppressive regimens were based on azathioprine and prednisone until the early 1980s, when cyclosporin became the mainstay of immunosuppressive therapy in combination with azathioprine and prednisone or prednisone alone. Approximately a decade later, tacrolimus was introduced. Tacrolimus and cyclosporin are both calcineurin inhibitors and are not used together. In the mid-1990s, mycophenolate mofetil (MMF) was introduced, which belongs to the anti-metabolite class of immunosuppressives, and this agent largely replaced azathioprine.[3] Recently, sirolimus has been introduced, an agent with yet a different mechanism of action and which, importantly, is not nephrotoxic like calcineurin inhibitors, although can potentiate their nephrotoxic effect.[4,5] Combinations of these agents increase options for tailoring immunosuppressive regimens to lower toxicities and improve graft survival.

Immunosuppressive regimens generally fall into three categories: (i) *induction regimens* are used in the first weeks post-transplant and use biological agents including anti-lymphocyte sera (polyclonal or monoclonal antibodies) or interleukin(IL)-2 receptor blockade; (ii) *antirejection regimens* treat episodes of rejection using high dosage, short-term treatment, typically with corticosteroids or anti-lymphocyte sera; and finally (iii) *maintenance regimens* provide long-term immu-

nosuppression with the goal of preventing acute rejection episodes, typically initiated soon after transplantation. With maintenance regimens, drug dosages are lowered over the first year of transplant to a baseline level. Most pregnant transplant recipients will be taking maintenance immunosuppressive therapy.

In 1991 the National Transplantation Pregnancy Registry (NTPR) was established at Thomas Jefferson University to study the safety of pregnancies in both female transplant recipients who become pregnant as well as male transplant recipients who father pregnancies. Entries to the registry to date in female recipients are summarised in table I. In 1997, the National Transplant Database Pregnancy Register was initiated to evaluate pregnancy outcomes in female transplant recipients in the UK.[6]

In the following sections, we briefly review the current agents with regard to their mechanisms and teratogenic risk, and examine pregnancy outcomes as well as the issue of the potential adverse effects of pregnancy on graft function. Analyses of data from reproductive studies of immunosuppressive regimens, from the Registries and from the literature, yield conclusions that impact on decisions about immunosuppression during pregnancy.

2. Commonly Used Immunosuppressive Agents and Teratology Concepts

Approximately 3 to 5% of the children born in the US manifest developmental defects and these birth defects can be attributed to a variety of causes. A majority are classified as having an unknown aetiology and it is estimated that only between 2 to 3% of these defects are classified as teratogen-induced malformations, considered to be the result of environmental or drug exposures during pregnancy.[7] One of the principles of teratology is that the susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which it interacts with the environment.[8] Thus, in the transplant population with multiple aetiologies of the original organ failure and multiple medication exposures, which include immunosuppressive agents, susceptibility will vary from patient to patient. Given the background incidence of malformations in the general population, assessing the incidence of malformations in the transplant population is fraught with difficulty. To date, case reports and registries have not observed a specific pattern or an increase in the incidence of malformations.

The US Food and Drug Administration (FDA) categorises drugs for pregnancy safety as: A, controlled studies, no risk; B, no evidence of risk in humans; C, risks cannot be ruled out; D, positive evidence of risk; and X, contraindicated. Most agents fall into category C where risks and benefits have to be weighed. Summaries of immunosuppressive agents and pregnancy information are listed in table II.[9]

2.1 Corticosteroids

Corticosteroids have broad anti-inflammatory and immunosuppressive effects, and are part of

Table I. Pregnancies in female transplant recipients from the National Transplantation Pregnancy Registry (NTPR) 2001

Organ	Recipients	Pregnancies	Outcomes[a]
Kidney	655	1003	1031
Liver	94	162	163
Liver-kidney	3	4	5
Pancreas-kidney	31	45	47
Heart	28	49	49
Heart-lung	3	3	3
Lung	12	13	13
Total	**826**	**1279**	**1311**

a Includes twins and triplets.

Table II. Immunosuppressive drugs commonly used in transplantation[9]

Drug	Usual oral dosage range (mg/kg/day)	Animal reproductive data?	Published pregnancy clinical outcomes?	FDA Pregnancy category
Corticosteroids				
prednisone, prednisolone	5-20 mg/d	Yes	Yes[a]	B
methylprednisolone	500-1000 mg/d (antirejection)	Yes	Yes[a]	B
Azathioprine	0.5-1.5	Yes	Yes[a]	D
Cyclosporin[b]	3-10	Yes	Yes[a]	C
Cyclosporin capsules USP (modified)[c]	3-10	Yes	No[a]	C
Tacrolimus	0.05-0.2	Yes	Yes[a]	C
Mycophenolate mofetil	2-3 g/d	Yes	Yes[a,d]	C
Muromonab-CD3 (OKT-3)	2.5-10 mg/d IV	No	Yes[a,d]	C
Antithymocyte globulin (Atgam®, ATG)[e]	15-30 mg/kg IV	No	Yes[d]	C
Antithymocyte globulin (Thymoglobulin®)[e]	1.0-1.5mg IV	No	No[a]	C
Sirolimus	2-5 mg/d	Yes	No[a]	C
Basiliximab	20 mg/d IV	Yes	No	B
Daclizumab	1 mg/kg IV	No	No	C

a Registry data.

b Novartis formulations.

c Generic microemulsion formulation of cyclosporin.

d Case reports only.

e The use of trade names is for identification purposes only and does not imply endorsement.

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

virtually all immunosuppressive regimens. Corticosteroid-associated adverse effects are numerous, including diabetes mellitus, aseptic necrosis of joints and peptic ulcer disease. Thus, steroid withdrawal as well as steroid avoidance attempts continue. An extensive survey of the literature analysed 468 cortisone-exposed, non-transplant gravidas and noted an overall fetal malformation rate of 3.5%, no greater than the general population.[10] Corticosteroids are of interest in animal studies, especially in mice, where they reproducibly cause cleft palate.[11] Corticosteroids have been implicated in increasing the risk of premature rupture of membranes[12] and causing adrenal insufficiency in newborns. Prednisone or prednisolone are used orally for maintenance therapy, and methylprednisolone is the intravenous form of the drug used for induction or treatment of rejection. They are classified as Category B agents and low teratogenic risk.[13]

2.2 Azathioprine

The introduction of azathioprine together with prednisone in 1962 created the reality of successful clinical kidney allograft transplantation and it still has some use today. Azathioprine is an inhibitor of purine metabolism and after absorption is rapidly converted in the liver into a number of metabolites. Its active metabolite, 6-mercaptopurine, has been found in cord blood.[14] Saarikoski and Seppala[15] suggested that the embryo might be protected against the effects of azathioprine because it lacked the enzyme inosinate pyrophosphorylase which converts 6-mercaptopurine to components that act on DNA in dividing cells. Before the introduction of cyclosporin, azathioprine was a primary drug used at dosages in the range of 1.5 to 3 mg/kg/day in conjunction with prednisone. Now, azathioprine is an adjunctive drug used at dosages of 0.5 to 1.5

mg/kg/day in combination with cyclosporin or tacrolimus ± prednisone.

While the teratogenicity of azathioprine has been noted in animal studies with embryonic resorption and/or fetal anomalies, clinical data so far have indicated only a small teratogenic risk, yet it is listed as a Category D agent.[13] In literature reviews, documented problems in the newborn include thymic atrophy, leukopenia, anaemia, thrombocytopenia, chromosome aberrations and reduced immunoglobulin levels along with infections and sepsis. Preterm delivery and intrauterine growth restriction have been noted but without any predominant structural malformation pattern.[16-19] In a case report in a kidney transplant recipient maintained on azathioprine and prednisone, chromosomal damage was noted in the newborn peripheral blood lymphocytes, which disappeared months later and of note, there were similar chromosomal aberrations in the mother herself.[20] Azathioprine use has decreased markedly with the availability of newer agents.

2.3 Cyclosporin

Cyclosporin, introduced in the early 1980s, rapidly became the mainstay of immunosuppression. This cyclic-11 amino acid peptide inhibits calcineurin, and thus blocks the transcription of cytokine genes necessary for T-cell activation and proliferation. The usual dosage range of cyclosporin is 3 to 10 mg/kg/day and in contrast to corticosteroids and azathioprine, is monitored by measuring blood concentrations, usually the trough concentration. Some data suggest that C_2 monitoring (2 hour post dose cyclosporin concentrations) is superior to following trough concentrations.[21] Toxicities include nephrotoxicity, hypertension, tremor, hypertrichosis and hyperlipidaemia. As cyclosporin only affects lymphocytes without depressing bone marrow or leucocyte counts, it is associated with a lower risk of infection than corticosteroids or azathioprine.[22-24]

Fetal toxicities and abnormalities in animal studies were noted at dosages higher than those in clinical use.[25,26] When first introduced, early reports raised concerns about the safety of its use in pregnancy.[27] Subsequently, clinical data have not indicated an increased incidence of congenital malformations and, in reviews of the literature, the consensus is that the magnitude of teratogenic risk for malformations is minimal, although with a moderate risk for fetal growth restriction.[13]

Cyclosporin is lipophilic with variable bioavailability. A microemulsion formulation (Neoral®)[1] was approved in 1995, which has decreased intra-patient and inter-patient variability and, therefore, provides more predictable pharmacokinetics.[28,29] There are now generic versions of this formulation available.

Cyclosporin is a Category C agent. It is also worth keeping in mind that most of the outcome data available include cyclosporin used together with azathioprine and prednisone.

2.4 Tacrolimus

Tacrolimus is a macrolide antibiotic approved in the US in 1995, which is a more potent calcineurin inhibitor than cyclosporin. Common adverse effects are nephrotoxicity, hypertension, neurotoxicity and diabetes mellitus.[30] As with cyclosporin, tacrolimus use in animal pregnancy studies revealed fetal resorptions at doses higher than expected in clinical use, whereas in the lower dosage group (0.16 mg/kg/day) fetuses that survived appeared no different than controls.[31] When compared with cyclosporin, a lower incidence of hypertension has been highlighted as potentially beneficial in pregnancy management,[32] as well as a lower incidence of hyperlipidaemia.[33] However, a higher incidence of diabetes and transient perinatal hyperkalaemia in the newborn has been noted.[32] Tacrolimus, like cyclosporin, is a Category C agent and, like cyclosporin, dosages are adjusted based on blood concentrations.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

2.5 Mycophenolate Mofetil

MMF, a category C agent, is a prodrug that undergoes hepatic ester hydrolysis to form the active metabolite mycophenolic acid, a reversible inhibitor of inosine monophosphate dehydrogenase, which blocks *de novo* purine synthesis on which lymphocytes are dependent. The toxicities of MMF are primarily gastrointestinal adverse effects and leukopenia. MMF was approved for use in the US in 1995 and is typically used in combination with a calcineurin inhibitor ± corticosteroids. The oral dosage range in adults is 2 to 3 g/day and blood measurements are not widely available.[34]

With regard to pregnancy safety, and in contrast to the calcineurin inhibitors, teratogenic risks are of concern based on the interpretation of reproductive toxicity studies in animals. Rats and rabbits exhibited developmental toxicity, malformations, intrauterine death or intrauterine growth retardation at doses which appear to be within recommended clinical doses based on body surface area.[35] Thus, there appears to be a possibility of increased risk in humans because there is no safety margin based on the animal studies. Data are accruing on the long-term benefits of this agent, so that one must weigh the potential risk of rejection and graft loss with discontinuation/switch against the potential risk for teratogenicity. MMF has, to a large extent, replaced azathioprine.

2.6 Sirolimus

Sirolimus, a category C agent, approved in the US in 1999, is a macrolide antibiotic with a novel mechanism of action. It has no effect on calcineurin activity but inhibits cytokine driven T-cell proliferation, thus preventing the progression from the G_1 to the S-phase of the cell cycle. This is at least two steps later in the cell activation/proliferation cascade than the calcineurin-dependent steps. In initial trials, sirolimus in combination with cyclosporin and prednisone provided enhanced immunosuppression and reduced acute rejection episodes.[4] Recommended dose administration for renal recipients is 2 mg/day for adults, adjusted for trough concentration. Decreased fetal weights and delayed ossification of skeletal structures were reported in animal studies, but no teratogenicity was noted. When administered in combination with cyclosporin to pregnant animals, there was increased fetal mortality, increased numbers of resorptions and decreased numbers of live fetuses, suggesting increased toxicity in conjunction with calcineurin inhibition.[36] Definitive clinical pregnancy outcome data are not yet available.

2.7 Other Agents

The agents listed in this section can be used transiently for 'rescue situations', such as the treatment of rejection, but have only a minor role with regard to pregnancy. Muromonab-CD3 (OKT-3), a category C agent, is a murine monoclonal IgG_{2A} antibody that binds to the CD3 antigen on human T cells, causing CD3+ cells to disappear from the peripheral circulation. It is used for induction or antirejection regimens.[9] No animal reproductive studies have been conducted. This is also the case for both antithymocyte globulin (polyclonal anti-human thymocyte sera produced from horses or rabbits)[9] and daclizumab, a humanised IgG_1 monoclonal antibody directed against the IL-2 membrane receptor.[35] Basiliximab, another IL-2 receptor antagonist, is a chimeric murine-human monoclonal antibody. Basiliximab and daclizumab are both produced by recombinant DNA technology and are only used as induction agents. In reproductive studies with basiliximab (Category B), no maternal toxicity, embryotoxicity or teratogenicity was observed in monkeys during the organogenesis period, even when blood concentrations were several times higher than those seen in humans.[37] However, IgG is known to cross the human placenta[38] and animal studies are not always predictive of human response.[39]

3. Pregnancy Outcomes

Is it reasonable to expect favourable pregnancy outcomes in this high-risk population given the myriad of comorbid conditions and immunosuppressive exposures? Surveys of the literature from

the azathioprine era in the 1970s and 1980s attest to thousands of successful post-transplant pregnancies. However, there was a spontaneous abortion rate of approximately 14%, with therapeutic terminations performed in a further 20% of conceptions. Of those conceptions that continued beyond the first trimester more than 90% were successful. For most women, renal function appeared to be augmented during pregnancy, but some degree of permanent impairment was apparent in approximately 15%, whilst in others there was evidence of transient deterioration, with or without proteinuria. Hypertension appeared to complicate approximately 30% of these pregnancies, with preterm delivery in approximately 45 to 60% and fetal growth restriction in about 20%. Caesarean sections were recommended for obstetric reasons only and neonatal complications included the sequelae of prematurity, including respiratory distress syndrome, as well as infection, but no predominant or frequent developmental anomalies.[40]

With the establishment of the NTPR in 1991 and the accumulation of cyclosporin data, analyses comparing cyclosporin-treated recipients with azathioprine-treated recipients could be conducted. These revealed a higher incidence of hypertension in the cyclosporin-treated recipients with lower mean birth weights (2407g with cyclosporin versus 2684g with azathioprine [non-cyclosporin]) and lower gestational ages (cyclosporin 35.6 weeks versus azathioprine [non-cyclosporin] 36.2 weeks), but again no predominant pattern of congenital malformations. Hypertension, shorter transplant to conception intervals and higher prepregnancy recipient creatinine levels were among the factors associated with lower birth weights. From a multivariate analysis, hypertension was the most significant of the pre- and peripartum pregnancy factors associated with lower birth weight in the newborns. [41]

3.1 Pregnancies with Calcineurin Inhibitors

Two extensive analyses of the two primary immunosuppressives, cyclosporin and tacrolimus, were recently published.[42,43] In the meta-analysis of cyclosporin-treated offspring from the Motherisk Program in Toronto, Ontario, Canada, the overall prevalence of malformations in the study population was 4.1% (14 out of 339 births), which was not felt to vary significantly from the general population.[42] The overall incidence of structural malformations in a recent analysis of NTPR cyclosporin-treated kidney and liver recipients (425 liveborn) was also in the 3 to 5% range with no predominant pattern of structural malformations. No structural malformations were noted in newborns of pancreas-kidney (21 liveborn), heart (27 liveborn) or lung recipients (3 liveborn).[44]

In 100 pregnancies analysed in 84 women treated with tacrolimus (83 transplant patients and one autoimmune disease), the women were grouped as follows: 66% liver, 27% kidney, 4% heart, 1% each kidney-pancreas, pancreas alone and lung. There were 71 pregnancies that progressed to delivery, 68 known to have resulted in live births. Of this group, 4 of the 71 (5.6%) had evidence of a structural malformation but, again, no specific pattern was evident.[43] In each of these reports there is some overlap with registry data. Table III compares registry reports with other reports in the literature.[32,45-48] Prematurity is a common outcome and newborn complications are generally more severe the shorter the gestation. Within each recipient group, a percentage experience graft dysfunction or graft loss (table IV, table V and table VI).

3.2 Safety of Pregnancy

One has to consider at the least the following two issues in evaluating pregnancies in the transplant population. Firstly, does pregnancy in and of itself adversely affect graft function? Secondly, is immunosuppression necessary during pregnancy to maintain graft function? We know that there is a relationship between immunity and pregnancy. For example, disorders associated with autoantibody production such as systemic lupus erythematosus may worsen during pregnancy, especially if active at conception, whereas other conditions such as rheumatoid arthritis may improve.[50,51] In patients with agammaglobulinaemia, the fetal im-

Table III. Comparison of pregnancy data reports in the literature and from the National Transplantation Pregnancy Registry (NTPR). Adapted from Armenti VT et al.[45]

Report	Recipients/ pregnancies	Immunosuppression	Pre-eclampsia (%)	Liveborn (%)	Mean GA (wks)	Mean BW (g)	Newborn complications (%)	Neonatal deaths (%)	Graft dysfunction/ rejection during pregnancy (%)	Recipient graft loss (%)
Kidney										
Toma et al.[46]	189/194	Cyclosporin-based 52% AZA-based 38% Tacro-based 0.5% Not reported 10%	24	82	35.7	2360	3[a]	1.4	19	13
NTPR[41]	115/154	Cyclosporin-based	25	69	35.6	2407	22	0.9	15	8[b]
	146/238	AZA-based 92% Steroid only 8%	21	83	36.2	2684	30	2.4	6	4[b]
Heart										
Branch et al.[47][c]	35/47	Cyclosporin-based	20	74	37	2543	20	0	24	26
Liver										
Jain et al.[32]	21/27	Tacrolimus-based	4	100[d]	36.6[e]	2638[e]	11	7	11	10
NTPR	15/21	Tacrolimus-based	5	76	37.4	3069	38	0	14	0[b]
NTPR	14/18	Cyclosporin-based[f]	24	72	36.9	2565	23	0	6	6[b]
Pancreas-Kidney										
Barrou et al.[48]	17/19	Cyclosporin-based	NR	100[d]	35	2150	11	0	0	12[g]
NTPR	18/23	Cyclosporin-based	25	87	34.8	2041	35	0	8.7	11[b,h]
Lung										
NTPR	6/6	Cyclosporin-based 5 Tacrolimus-based 1	0	50	32.8	2202	67	0	33	17[b]

a Newborn malformations.

b Graft loss within 2 years of delivery.

c International review including NTPR data.

d Only livebirths reported.

e Neonatal deaths excluded from analysis.

f Microemulsion formulation - Novartis.

g One kidney and one pancreas loss in two different recipients.

h One kidney and one pancreas/kidney loss in two different recipients.

AZA = azathioprine; **BW** = birthweight; **GA** = gestational age; **NR** = not reported.

Table IV. Pregnancy outcomes in female kidney recipients from the National Transplantation Pregnancy Registry (reproduced from Armenti VT et al.[44] with permission)

Parameter	Cyclosporin[a]	Microemulsion formulation cyclosporin[b]	Tacrolimus[c]
Maternal factors (% pregnancies)			
Transplant to conception interval	3.3y	4.9y	2.2y
Hypertension during pregnancy (%)	63	73	47
Diabetes during pregnancy (%)	12	7	13
Infection during pregnancy (%)	23	24	35
Rejection episode during pregnancy (%)	4	2	14
Pre-eclampsia (%)	30	23	37
Mean serum creatinine (mg/dl)			
before pregnancy	1.4	1.3	1.3
during pregnancy	1.4	1.4	1.8
after pregnancy	1.6	1.5	1.7
Graft loss within 2y of delivery (%)	9	3	17
Outcomes (n)[d]	**(487)**	**(113)**	**(39)**
Therapeutic abortions (%)	8	2	3
Spontaneous abortions (%)	12	18	21
Ectopic (%)	1	0	0
Stillborn (%)	3	1	3
Livebirths (%)	76	80	74
Livebirths (n)	**(369)**	**(90)**	**(29)**
Mean gestational age (wks)	36	36	34
Mean birthweight (g)	2493	2416	2104
Premature (% <37 wks)	52	56	57
Low birthweight (% <2500g)	45	54	66
Caesarean section (%)	52	43	56
Newborn complications (%)	40	50	52
Neonatal deaths, no. (%) [within 30 days of birth]	3 (1)	0	1 (3)

a Novartis formulation (320 recipients, 478 pregnancies).
b Novartis formulation (83 recipients, 108 pregnancies).
c Tacrolimus (30 recipients, 38 pregnancies).
d Includes twins, triplets.

mune system develops independently of the mother's, and infants born to mothers with this condition have normal immunological maturation, despite the lack of circulating maternal antibodies.[52]

Case control studies that compared transplant recipients who became pregnant to those recipients who did not strongly suggest that pregnancy in and of itself did not cause serious deterioration in graft function in the presence of stable prepregnancy graft function and, at worst, there might be a minor deleterious effect.[53-56] In contrast, one study has suggested that pregnancy had an adverse effect on graft function but the control group had 100% graft survival.[57] From NTPR data, female kidney recipients have mean postpartum serum creatinine levels slightly higher overall than mean prepregnancy levels, even when patients with rejection during pregnancy are excluded.[49] Pregnancy may deleteriously affect graft function unpredictably but is more likely to have an impact in the setting of prepregnancy graft dysfunction. This is illustrated by an NTPR analysis where it was noted that a group of cyclosporin-treated renal recipients with a high mean serum creatinine level prepregnancy (≥2.5 mg/dl) were three times more likely to experience graft loss postpartum than those recip-

Table V. Pregnancy outcomes in liver recipients from the National Transplantation Pregnancy Registry (reproduced from Armenti VT et al.[44] with permission)[a]

Parameter	Cyclosporin[b]	Microemulsion formulation cyclosporin[c]	Tacrolimus[d]
Maternal factors (% pregnancies)			
Transplant to conception interval (y)	3.4	6.1	2.8
Hypertension during pregnancy (%)	41	40	28
Diabetes during pregnancy (%)	2	0	16
Infection during pregnancy (%)	33	36	10
Rejection episode during pregnancy (%)	14	8	6
Pre-eclampsia (%)	26	32	11
Graft loss within 2y of delivery (%)	9	11	0
Outcomes (n)[e]	**(92)**	**(26)**	**(32)**
Therapeutic abortions (%)	10	0	0
Spontaneous abortion (%)	13	27	25
Ectopic (%)	0	0	0
Stillbirth (%)	3	0	3
Live births (%)	74	73	72
Live births (n)	**(68)**	**(19)**	**(23)**
Mean gestational age (wks)	37	38	37
Premature (% <37 wks)	37	26	39
Mean birthweight (g)	2686	2715	2827
Low birthweight (% <2500g)	32	37	26
Caesarean section (%)	43	21	35
Newborn complications (%)	25	26	30
Neonatal deaths (% within 30 days of birth)	0	0	0

a Eight recipients had subsequent pregnancies on different regimens.
b Novartis formulation (58 recipients, 91 pregnancies).
c Novartis formulation (19 recipients, 26 pregnancies).
d Tacrolimus (21 recipients, 32 pregnancies).
e Includes twins.

ients with a mean serum creatinine level of <1.5 mg/dl.[58] Similarly, data from the UK National Register also identified lower prepregnancy serum creatinine levels as a favourable predictor for pregnancy outcome.[59] The presence of chronic rejection prepregnancy has been identified as a risk for pregnancy-related graft deterioration.[60]

Conclusions have been drawn largely from analyses of the renal population and to some degree extrapolated to other organ recipients. Although the numbers of pregnancies in non-renal recipients are accruing but do not yet allow the same detailed evaluation, some conclusions can still be drawn. The importance of adequate stable graft function is illustrated in an NTPR study that compared the outcomes of pregnancies in female liver recipients with biopsy proven rejection versus pregnancies with no rejection episodes. From 119 pregnancies in 72 female liver recipients with 91 livebirths, biopsy proven rejection occurred in ten recipients (11 pregnancies), treated with methylprednisolone (n = 8), muromomab-CD3 (n = 1), anti-lymphocyte serum (n = 1) and corticosteroids with an increase in tacrolimus (n = 1). Birthweights were lower in the newborn of the rejection group compared with the no rejection group (2807g vs 1946g, p = 0.006). Also of note, biopsy proven rejection occurred within the first 3 months postpartum in 11 female recipients, of whom 45% had rejection during pregnancy, underscoring the poorer

newborn and maternal outcomes in the setting of rejection.[49] In addition, in an analysis of registry data, liver recipients with recurrent hepatitis C appeared to be at risk for peripartum graft dysfunction with subsequent pregnancies.[61]

Two groups of pancreas-kidney recipients, with and without postpartum graft loss were analysed. Significant differences between the groups were found in mean serum creatinine levels, both during pregnancy (graft loss 2.23 mg/dl versus no graft loss 1.49 mg/dl; p = 0.013) and postpartum (graft loss 2.51 mg/dl versus no graft loss 1.53 mg/dl; p = 0.013), and in rejection episodes during pregnancy (graft loss three of eight versus no graft loss 0 of 28; p = 0.008).[62]

If pregnancy in transplant recipients is not contraindicated then the goal must be to maintain stable graft function throughout pregnancy. As noted

Table VI. Pregnancy outcomes in female recipients of organs other than kidney or liver from the National Transplantation Pregnancy Registry. Adapted from Armenti VT et al.[49]

Parameter	Pancreas/kidney (27 recipients)	Heart (24 recipients)	Lung (10 recipients)
Maternal factors (% pregnancies)			
Hypertension during pregnancy (%)	82	47	64
Diabetes during pregnancy (%)	0	2	18
Graft dysfunction during pregnancy (%)	18		
Infection during pregnancy (%)	58	14	18
Rejection episode during pregnancy (%)	9	24	36
Pre-eclampsia (%)	48	10	0
Graft loss within 2y of delivery (%)	19	0	30
Outcomes (n)[a]	**(37)**	**(43)**	**(11)**
Therapeutic abortions (%)	8	12	36
Spontaneous abortion (%)	8	21	9
Ectopic (%)	3	2	0
Stillbirth (%)	0	0	0
Live births (%)	81	65	55
Live births (n)	**(30)**	**(28)**	**(6)**
Gestational age (wks; mean)	34	37	34
Birthweight (g; mean)	2075	2703	2149
Premature (% <37 wks)	80	43	67
Low birthweight (% <2500g)	67	36	67
Caesarean section (%)	57	29	50
Newborn complications (%)	57	29	83
Neonatal deaths (% within 30 days of birth)	3[b]	0	0
Immunosuppression during pregnancy[c]			
Cyclosporin[d], AZA, prednisone (%)	51	70	55
Cyclosporin[d], prednisone (%)	17	14	9
Cyclosporin[e], AZA, prednisone (%)	17	7	9
Cyclosporin[e], prednisone (%)	3		
Tacrolimus, AZA, prednisone (%)	6	5	18
Tacrolimus, AZA (%)	3		
Tacrolimus, prednisone (%)		2	
Tacrolimus alone (%)		2	9

a Includes twins.
b One neonatal death due to sepsis.
c For pancreas/kidney, numbers do not add up to 100 due to rounding.
d Novartis formulation.
e Novartis microemulsion formulation.
AZA = azathioprine.

previously, within each of the organ recipient groups reported to the NTPR, a small percentage have had pregnancies complicated by rejection, endorsing the hypothesis that immunosuppression must be maintained during pregnancy. The risks of potential teratogenicity have to be accepted because withdrawal of immunosuppression during pregnancy would adversely affect graft function and pregnancy outcome.

Summarised in table VII are changes in immunosuppression dose administration during pregnancy as reported to the NTPR.[49] As a result of altered physiology during pregnancy, doses may need to be adjusted to remain in the therapeutic range. In an earlier case control study from the NTPR of cyclosporin-treated kidney recipients, comparing two groups, stable graft function versus graft dysfunction, those recipients with stable graft function in fact received higher cyclosporin dosages prepregnancy and throughout pregnancy when compared with the group with graft dysfunction.[63]

Regarding other risks to the fetus, table IV, table V and table VI summarise pregnancy outcomes reported to the registry, including details of immunosuppression regimens.[44,49] Overall, there is a higher incidence of prematurity and low birth weight compared with the general population; many pregnancies are complicated by hypertension and preeclampsia, and a small number are complicated by rejection and peripartum graft deterioration. Of note, compared with cyclosporin, in tacrolimus-treated liver recipients there is a trend for a lower incidence of hypertension and preeclampsia, but in kidney recipients a trend toward lower birthweights.

Continued analyses of cyclosporin- and tacrolimus-treated offspring are in progress. Most newborn complications are related to prematurity with no predominant pattern or increase in malformations. Of note is a case in a tacrolimus-treated renal recipient where a twin birth occurred and cardiomyopathy occurred in the twins, raising concern as to whether this was a cardiotoxic effect of tacrolimus.[64] No other similar cases have been reported to the registry. To date, we are aware of seven female kidney recipients with 11 pregnancies (seven livebirths, four spontaneous abortions) with some exposure to MMF in combination with cyclosporin or tacrolimus.[44,65] In a case recently reported to the NTPR complicated by rejection at 24 weeks, treatment also involved in addition to MMF and tacrolimus, corticosteroids, antithymocyte globulin, and initiation of sirolimus, and the newborn was reported to have a cleft lip and palate and ear deformity.[44]

3.3 Breastfeeding and Outcomes of Children

Follow-up of children of recipients has been encouraging. Despite theoretical risks to the fetus there have been no reports of significant impaired immune or renal function,[66-68] and NTPR data in cyclosporin-treated kidney recipient offspring revealed no increase over the general population in the expected number of children with developmental delay.[69]

Table VII. Immunosuppressive dose adjustments during pregnancy in female kidney recipients (reproduced from Armenti VT et al.[49] with permission)

Adjustment	Cyclosporin [no. pts (%)][a]	Tacrolimus [no. pts (%)][b]
Increased dose	26 (44)	5 (22)
Varied dose	7 (12)	2 (9)
Decreased dose	0 (0)	1 (4)
No change	19 (32)	12 (52)
Switched agents	7 (12)	2 (9)
Discontinued agent	0 (0)	1 (4)

a Novartis microemulsion formulation (59 pregnancies).

b 23 pregnancies.

Some recipients have chosen to breastfeed.[70] The limited evidence in the literature must be interpreted depending on one's personal threshold for accepting some exposure of the newborn to immunosuppressants.[61,71] Limited numbers of entries to the NTPR have not revealed specific problems but more follow-up is needed.

Some authors have warned of the potential of lingering effects into the next generation.[72] Ongoing follow-up of cyclosporin-treated offspring, some now approaching reproductive age, as well as offspring of the newer recipient regimens are goals of the NTPR. Two separate issues to be considered are: (i) the recipient's underlying disease and the increased risk of having newborns with growth restriction and prematurity; and (ii) the risk of complications and/or mortality among the transplant recipient parents of these children and the effects on child rearing. Given the complexity of the transplant recipient population, it may be more appropriate to consider this population as defining its own outcomes rather than to compare them to the general population.

4. Summary: Choice of Immunosuppressive Agent

In the early years of transplantation, there were no options for immunosuppression. Now there are choices in implementing and tailoring immunosuppressive regimens.[73-75] Should a regimen be specifically designed for the patient of childbearing age or for consideration for pregnancy? Of note, in the criteria from 1976 was the recommendation to continue maintenance immunosuppression, which still applies today. Extensive pregnancy data on azathioprine- and cyclosporin-treated recipients are already available, but nowadays recipients also have the option of regimens which include newer agents such as sirolimus and/or MMF, whether given for maximal immunosuppression, calcineurin inhibitor minimisation, or steroid minimisation or withdrawal. Over time, there has been steady improvement in patient and graft survival rates, associated with a shift in the use of immunosuppressives toward newer agents.[76] Thus, it is becoming unlikely for a clinician today just to use cyclosporin and prednisone with or without azathioprine, even though it is the regimen with the greatest pregnancy experience, because if optimal graft function is to be achieved then the best combination of agents available should be given to ensure this. The newer agents may have limited reproductive and/or clinical pregnancy data available, so unknown potential for teratogenicity exists. In some patients, given the information available, some centres have chosen to switch patients from MMF to azathioprine (pre- and post-conception) or reduce the MMF dosage because of the concerns of MMF exposure during pregnancy.

The incidence of structural malformation has not been noted to be increased compared with the general population but newer combinations are yet to be evaluated. Risk of rejection must be weighed against potential teratogenicity. Rejection must be avoided, as it is associated with poorer outcomes for mother and child. Prednisone at low doses has not been problematic in pregnancy, yet current clinical regimens are often directed toward avoidance or withdrawal. Steroid avoidance or withdrawal regimens will necessarily expose the recipient to agents for which there is less pregnancy safety information.

In conclusion, no one immunosuppressive regimen has been identified as being superior to another for use during pregnancy. Sporadic cases of rejection, graft dysfunction, graft deterioration and poor pregnancy outcome have been noted with all regimens. Continued close surveillance and collaboration, evaluation through case publications, centre reports and registry analyses should continue to help caretakers involved in the management of the pregnant transplant patient.

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