The first child born to a transplant recipient turned 48 years old on March 10, 2006. When the field of transplantation was first developing, physicians worried about the teratogenicity of immunosuppressive medications and considered pregnancy ill-advised. Despite early concerns, approximately 14,000 births among women with transplanted organs have been reported worldwide, and many more have assuredly occurred. Pregnancy is now an expected part of the benefits afforded to women by organ transplantation.

However, substantial gaps remain in our knowledge about pregnancy in the transplant recipient and its effects on the child. As discussed in an article by Ross that appears in this issue of the Journal, ethical concerns have been raised about the wisdom of pregnancy for a woman who might have a limited life span or in whom serious medical complications might develop.

Sources of Information about Pregnancy in Transplant Recipients
Information about pregnancy in recipients of solid-organ transplants comes primarily from voluntary registries, case reports, and retrospective center studies. Three registries offer data about pregnancy outcomes: the National Transplantation Pregnancy Registry in the United States, the European Dialysis and Transplant Association Registry, and the UK (United Kingdom) Transplant Pregnancy Registry. Table 1 indicates that all three registries show similar trends in miscarriages, therapeutic terminations, stillbirths, ectopic pregnancies, preterm births, low-birthweight babies, and neonatal deaths (also see Fig. 1 and 2). The guidelines for management of pregnancy after transplantation are generally derived from retrospective reports and registry-based data.

Fertility, End-Stage Disease, and Transplantation
Women with end-stage kidney disease have hypothalamic–gonadal dysfunction and infertility. Improvements in dialysis have lessened hormonal dysfunction in women undergoing dialysis, but most remain infertile. Female infertility also occurs with end-stage disease of other organs, including the heart, liver, and lung. Nevertheless, all women with end-stage organ disease who are of childbearing age need effective contraception, since unwanted pregnancies may occur occasionally.

Within the first months after transplantation, gonadal dysfunction rapidly reverses and female fertility returns, conferring a substantial possibility of conception. Whether fertility returns to normal is still unknown. Given these facts, counseling about reproductive potential should occur before transplantation. The choice of contraceptive method is somewhat arbitrary and is best determined by the efficacy of the method and the likelihood of patient adherence. Barrier methods are no longer considered optimal because of the necessity for consistent use. Many physicians prescribe long-acting forms of contraception to ensure effective
Intrauterine devices are more likely to fail in patients taking immunosuppressive agents, because their efficacy depends on intact immunologic function. Intrauterine devices may also increase the risk of intrauterine infections.

**Optimal Timing of Pregnancy after Transplantation**

Most transplantation centers have advised that conception is safe after the second post-transplantation year, on the assumption that the graft functions well (in a kidney transplant, for example, stable serum creatinine level of 1.5 mg per deciliter [133 μmol per liter] or less and a rate of urinary protein excretion less than 500 mg per day are arbitrarily defined as indicating that a renal allograft is functioning well). Guidelines have not been established for recipients of other solid organs. A consensus conference held by the Women's Health Committee of the American Society of Transplantation in March 2003 concluded that pregnancy is usually safe after the first year, provided that allograft function is stable and that no rejection episodes have occurred in the year before conception. At that point, the risk of a rejection episode is generally low, the dose of immunosuppressive medication is at its nadir, viral prophylaxis has been completed, and the patient is generally stable.

All pregnancies in solid-organ–transplant recipients should be considered high risk and should be managed by a multidisciplinary team. The expectant mother should be monitored closely (at least every two weeks) by her transplantation physician, and her prenatal care should preferentially be managed by a specialist in high-risk obstetrics (maternal–fetal medicine). Cesarean delivery is indicated only for obstetrical reasons.

Patients should also receive careful and frequent follow-up from their transplantation physicians during the puerperium and subsequent weeks so that their allograft function and serum
levels of immunosuppressive drugs can be monitored closely. A neonatologist should be involved in case of unexpected problems with the baby. Ideally, the pregnant transplant recipient would consult with the neonatologist and the pediatrician before delivery to prepare for any immediate or long-term issues.

**RISK OF PREGNANCY COMPLICATIONS IN THE TRANSPLANT RECIPIENT**

Many recipients of solid-organ transplants have hypertension and some degree of renal dysfunction; both conditions are independently associated with a high risk of pregnancy complications. The risk is also increased by the use of immunosuppressive medications; for example, calcineurin inhibitors are associated with hypertension, diabetes mellitus, kidney dysfunction, and lower mean birth weight (Table 2).

**Hypertension and Preeclampsia in Pregnant Kidney-Transplant Recipients**

The incidence rates of hypertension and preeclampsia among transplant recipients vary with the type of solid organ received. Since hypertension is common in transplant recipients receiving calcineurin inhibitors, it is not surprising that the National Transplantation Pregnancy Registry has reported hypertension rates of 47 to 73 percent in pregnant kidney-transplant recipients (Table 2). Lower rates have been reported for pregnant women who have received liver, heart, or lung transplants (Table 3).

Preeclampsia rates also vary among recipients, depending on the organs transplanted (Table 3). Preeclampsia has been reported to develop in approximately one third of pregnant women receiving kidney or pancreas–kidney transplants, whereas lower rates have been reported in liver, heart, and lung recipients. Diagnosing preeclampsia accurately is difficult, because blood pressure frequently increases after the 20th week of gestation and many transplant recipients have preexisting proteinuria. Furthermore, calcineurin inhibitors increase uric acid levels, rendering an elevated uric acid level, which is usually a helpful marker for diagnosing preeclampsia, less reliable. Other serum markers of preeclampsia (e.g., alterations in levels of circulating angiogenic and antiangiogenic proteins) may facilitate distinguishing preeclampsia from other conditions in pregnant recipients of solid-organ transplants.

Hypertension can cause preterm delivery and may explain, at least in part, why half of all pregnancies in such transplant recipients end in preterm delivery. Although no consensus exists regarding treatment of mild-to-moderate hypertension in normal pregnancy, there is agreement that hypertension in pregnant transplant recipients requires aggressive treatment. Several antihypertensive agents deserve comment. Methyldopa is still considered a safe and preferred agent, since it has been used for decades to treat pregnancy-related hypertension. Second-line agents that are used include combined α- and β-adrenergic blockers, calcium-channel blockers, α-adrenergic blockers, and thiazide diuretics. Thiazide diuretics need not be discontinued if they were used before conception. Angiotensin-converting–enzyme inhibitors and angiotensin-receptor blockers, drugs that interfere with the renin–angiotensin system, are associated with fetopathy and are contraindicated after the first trimester.

![Figure 1. Pregnancies in Kidney-Transplant Recipients Reported Worldwide.](image-url)
Hypertension and Preeclampsia in Pregnant Recipients of Other Solid-Organ Transplants

Table 3 summarizes pregnancy complications in recipients of other solid organs. Hypertension, preeclampsia, preterm delivery, and low-birth-weight infants may complicate pregnancy in patients with liver, heart, or lung allografts.\textsuperscript{13,49,50,56} Patients with liver or heart transplants are less likely to have premature births than kidney-transplant recipients, and the mean birth weights and maturity of their infants are greater.\textsuperscript{47,56} Recipients of heart or lung transplants are more likely to have rejection episodes during pregnancy than are recipients of other organs\textsuperscript{57}; however, the rate of detection of rejection episodes may be higher in heart and lung recipients because these patients undergo routine biopsies of their allografts.

Risk of Allograft Loss

In women with preexisting renal dysfunction (serum creatinine level greater than 1.5 mg per deciliter), the risk of irreversible loss of renal-allograft function is increased during and after pregnancy.\textsuperscript{42} The risk is lower if the serum creatinine level is less than 1.5 mg per deciliter at the time of conception.\textsuperscript{9,11,58-60} One case–control study showed that the rate of allograft survival at 10 years was lower in women who had given birth after receiving the allograft than among women who had never been pregnant.\textsuperscript{61} However, the results of this study have been criticized because the control group had unusually high graft survival at 10 years (100 percent), whereas those who had given birth had allograft survival rates typical of most centers during the study period (1971 to 1991). There are no long-term controlled studies examining glomerular filtration rates and proteinuria in women with kidney transplants who have become pregnant.

Allograft loss within two years after pregnancy among recipients of liver, heart, lung, and pancreas–kidney transplants is shown in Table

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**Figure 2.** Number of Pregnancies Reported to the National Transplantation Pregnancy Registry in Recipients of Kidney Transplants and in Recipients of Other Organ Transplants.

The number of pregnancies in kidney-transplant recipients far exceeds that in recipients of other organs.\textsuperscript{7,13,21-24} Data were not reported in 1998.
Pregnancy in patients with lung transplants has been associated with allograft deterioration, but the reasons for the deterioration are unclear and the number of patients is small. One article reported five pregnancies among stable lung-transplant recipients. No deterioration was observed in four recipients, but one had a decline in pulmonary function and terminated the pregnancy.

Adverse outcomes have also been reported among pregnant liver-transplant recipients with a pretransplantation history of viral hepatitis; however, this finding may represent only a coincidence. The National Transplantation Pregnancy Registry reported four maternal deaths among 44 pregnant liver-allograft recipients. Three of these deaths were due to post-transplantation progression of viral hepatitis (hepatitis C and hepatitis B).

**Pregnancy and the Risk of Rejection**

Maintaining appropriate blood levels of immunosuppressive medications may be challenging during pregnancy. For example, calcineurin-inhibitor dosing may require adjustment because the circulating drug levels fluctuate with the changing volume of distribution and alterations in extracellular volume that accompany gestation. Case–control studies of immunosuppressive levels in pregnant recipients of solid-organ transplants have not been performed to evaluate whether immunosuppression must be maintained at prepregnancy levels. One case report documented rejection associated with a fall in blood levels of cyclosporine during gestation in a previously stable lung-transplant recipient. National Transplantation Pregnancy Registry data indicate that pregnant kidney-transplant recipients who maintained stable function during their pregnancies took higher doses of cyclosporine before and during pregnancy than patients who had renal dysfunction. In contrast, Jain et al. reported no rejection episodes in a retrospective analysis of 21 pregnancies in kidney and kidney–pancreas recipients in whom tacrolimus levels were not adjusted during gestation, despite the presence of decreased trough levels. The limited data available suggest that drug levels still provide the best guide for maintaining adequate immunosuppression during pregnancy.
ing gestation should not occur, given the natural, nonspecific, systemic maternal immunosuppression that exists to prevent maternal rejection of the fetus. However, available reports indicate that the rejection rates in pregnant recipients of solid-organ transplants are similar to those in nonpregnant recipients. The fetus expresses both parents’ histocompatibility antigens and is therefore allogeneic, or foreign, with respect to the mother. Much recent work suggests that the fetus is protected from rejection by potent immunoregulatory mechanisms at the maternal–fetal interface, those that are specific to paternal antigens, or both. Reduction of immunosuppressive medications during pregnancy, based on the premise of natural nonspecific maternal immunosuppression, may lead to rejection of transplanted organs. Two maternal deaths have, in fact, been reported as due to discontinuation of immunosuppressive medications during pregnancy.

Allograft dysfunction may be difficult to detect during pregnancy. One reason is that creatinine levels normally decrease during gestation due to enhanced glomerular filtration rates; thus, during pregnancy, renal-allograft rejection may be signaled by only a small rise in the serum creatinine level. Acute rejection episodes during gestation usually respond to methylprednisolone. Treatment with muromonab-CD3 (Orthoclone OKT3), antithymocyte globulin (ATG, ATGAM), daclizumab (Zenapax), or basiliximab (Simulect) may be effective, but none of these agents are advocated as first-line rejection treatment during pregnancy, given the limited data about their safety and effectiveness in this setting.

**IMMUNOSUPPRESSIVE MEDICATIONS AND THE MATERNAL–FETAL CIRCULATION**

The maternal–fetal circulation includes the placenta, umbilical vein, and fetal inferior vena cava. All medications used to prevent rejection of transplanted organs cross the maternal–placental–fetal interface. Because of the unique position of the fetal liver between the umbilical vein and the fetal inferior vena cava, it filters all pharmacologic agents that pass through the placenta. Fetal drug distribution is determined by complex pharmacokinetic and pharmacodynamic factors that are influenced by the solubility of the drug, its molecular weight, and the metabolism of the drug by enzyme systems that are differentially expressed in placental and fetal tissues and change throughout ontogeny. The difficulty of determining drug distribution in the fetal–maternal circulation and within the fetus may explain conflicting results in reports of fetal exposure to immunosuppressive agents.

Prednisone, dexamethasone, and cortisol easily traverse the placenta, but 90 percent of the maternal dose is metabolized within the placenta before reaching the fetus. Methylprednisolone also crosses the placenta, but it is metabolized

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**Table 3. Characteristics of Pregnancy among Transplant Recipients during Pregnancy and of Their Infants, According to Organ Received.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Kidney†</th>
<th>Liver‡</th>
<th>Pancreas and Kidney§</th>
<th>Heart‡</th>
<th>Lung‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of recipients</td>
<td>751</td>
<td>106</td>
<td>37</td>
<td>39</td>
<td>13</td>
</tr>
<tr>
<td>No. of pregnancies</td>
<td>1139</td>
<td>182</td>
<td>53</td>
<td>63</td>
<td>14</td>
</tr>
<tr>
<td>Hypertension during pregnancy (%)</td>
<td>28–72</td>
<td>22–42</td>
<td>75</td>
<td>47</td>
<td>50</td>
</tr>
<tr>
<td>Diabetes during pregnancy (%)</td>
<td>3–12</td>
<td>0–13</td>
<td>2</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>Rejection episodes (%)</td>
<td>2–12</td>
<td>0–11</td>
<td>6</td>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>Preeclampsia (%)</td>
<td>29–31</td>
<td>13–33</td>
<td>33</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Graft loss within 2 yr (%)</td>
<td>4–14</td>
<td>3–9</td>
<td>17</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>Live birth (%)</td>
<td>71–78</td>
<td>72–82</td>
<td>80</td>
<td>70–80</td>
<td>57</td>
</tr>
<tr>
<td>Mean duration of gestation (wk)</td>
<td>35–36</td>
<td>37–38</td>
<td>34</td>
<td>37–38</td>
<td>35</td>
</tr>
<tr>
<td>Mean birth weight of infant (g)</td>
<td>2308–2493</td>
<td>2635–2802</td>
<td>2128</td>
<td>2717–2930</td>
<td>2285</td>
</tr>
<tr>
<td>Cesarean section (%)</td>
<td>46–92</td>
<td>22–42</td>
<td>52</td>
<td>29–100</td>
<td>38</td>
</tr>
</tbody>
</table>

* The ranges indicate the values reported from different studies.
† Data are from Armenti et al. and Miniero et al.
‡ Data are from Armenti et al.
§ Data are from Armenti et al. and Miniero et al.
efficiently and detected only at low levels in the fetal circulation. Efficient placental metabolism of corticosteroids may protect the fetus from adverse effects, although sporadic cases of fetal adrenal suppression have been reported.

Azathioprine passes into the fetal circulation, but one report found only inactive metabolites in a pregnant woman receiving this drug, a result suggesting that the fetus lacks inosinate pyrophosphorylase, an enzyme required to convert azathioprine to its active metabolite, 6-mercaptopurine. The calcineurin inhibitors cyclosporine (Neoral, Sandimmune, Gengraf) and tacrolimus (Prograf), which are mainstays of maintenance immunosuppressive therapy in transplantation, readily cross the placenta and enter the fetal circulation. Cyclosporine is detected in the amniotic fluid, placenta, and fetal tissue; the levels may be higher in the placenta and umbilical cord than in the maternal circulation. However, the blood levels of calcineurin inhibitors in the fetus have been reported to be half the levels in the mother. One study noted that the serum of a newborn inhibited T cells in culture to the same degree as the mother’s serum, an observation suggesting that cyclosporine in fetal blood confers potent immunosuppressive properties.

**IMMUNOSUPPRESSIVE MEDICATIONS AND THE FETUS**

Since immunosuppressive medications must be continued throughout pregnancy, the fetus is inevitably exposed to potential fetotoxic and teratogenic agents through development. The actual effects of medications on ontogeny and growth may be difficult to determine and may not be obvious at birth. It may also be difficult to assess the relative effects of immunosuppressive agents, since the diagnoses of underlying maternal diseases as well as the concurrent use of other medications inevitably confound associations.

Potential adverse effects associated with immunosuppressive medications range from major malformations to subtle defects such as immunologic or neurocognitive defects that are not evident until several years after birth. The risk of major malformations from immunosuppressive medications must be put into the context of the risk from other drugs that have teratogenic effects. Not all teratogenic drugs cause defects in all exposed infants. For example, the well-known teratogenic effect of thalidomide occurred in only 20 percent of babies whose mothers used the drug during the critical teratogenic period. Subtle defects induced by immunosuppressive agents may be impossible to detect by observational studies. Randomized trials to evaluate the safety of medications during pregnancy in recipients of solid-organ transplants cannot be designed easily, for both ethical and practical reasons involving a clear risk of rejection. Thus, at present observational studies guide clinical decisions, although the low prevalence of adverse outcomes makes such studies difficult to interpret and subject to bias.

The Food and Drug Administration (FDA) has developed a classification that codifies the safety categories of immunosuppressive medications (Table 4). These categories are A (no human risk), B (animal studies showing risk, but no evidence of human risk), C (human risk not ruled out), D (evidence of human risk), and X (absolutely contraindicated). These categories are difficult to interpret and to apply in the setting of pregnant recipients of solid-organ transplants, particularly since many of the data are not derived from pregnant women. For instance, azathioprine is designated as category D on the basis of observations of skeletal, visceral, and hematologic abnormalities in rodent fetuses, as well as reports of human fetal immunosuppression and structural malformations (one in a fetus of a mother taking azathioprine and another in an infant whose father was a transplant recipient). However, despite the category D designation, the transplantation community has not recommended that transplant recipients should avoid taking azathioprine during pregnancy.

Newer immunosuppressive drugs are rated as category C, because human studies evaluating safety during pregnancy were not performed before the drug was released.

<table>
<thead>
<tr>
<th>TOXIC EFFECTS OF IMMUNOSUPPRESSIVE AGENTS IN PREGNANCY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STRUCTURAL MALFORMATIONS IN ANIMAL MODELS</strong></td>
</tr>
<tr>
<td>There are few data to inform the clinician about the toxic effects of various immunosuppressive agents in human fetuses. However, studies of gestation in rodents provide important clues to potential toxic effects of immunosuppressive medications in human neonates. Although all toxic...</td>
</tr>
</tbody>
</table>
The FDA categories are defined as follows: A (not listed here) indicates that induction therapy is used within the first hours to weeks after transplantation. B indicates that no evidence of risk in humans has been found — studies in animals show risk whereas in humans controlled human studies show no risk. C indicates that human risk cannot be ruled out — studies in humans are lacking and studies in animals are either positive for risk or lacking. D indicates evidence of human risk. X (not listed) signifies that the use of the drug is contraindicated during pregnancy. Studies in animals or humans (or investigational or post-marketing reports) have demonstrated fetal risk that outweighs any potential benefit.

<table>
<thead>
<tr>
<th>Type of Therapy*</th>
<th>FDA Category†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td></td>
</tr>
<tr>
<td>Muromonab-CD3 (Orthoclone OKT3)</td>
<td>C</td>
</tr>
<tr>
<td>Daclizumab (Zenapax)</td>
<td>C</td>
</tr>
<tr>
<td>Basiliximab (Simulect)</td>
<td>B</td>
</tr>
<tr>
<td>Antithymocyte globulin (Thymoglobulin)</td>
<td>C</td>
</tr>
<tr>
<td>Antithymocyte globulin, antilymphocyte globulin (ATGAM, ATG)</td>
<td>C</td>
</tr>
<tr>
<td>Maintenance</td>
<td></td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine (Neoral, Sandimmune, Gengraf)</td>
<td>C</td>
</tr>
<tr>
<td>Tacrolimus (Prograf)</td>
<td>C</td>
</tr>
<tr>
<td>Antiproliferative agents</td>
<td></td>
</tr>
<tr>
<td>Mycophenolate mofetil (CellCept, Myfortic)</td>
<td>C</td>
</tr>
<tr>
<td>Azathioprine (Imuran)</td>
<td>D</td>
</tr>
<tr>
<td>Sirolimus (formerly called rapamycin; Rapamune)</td>
<td>C</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>B</td>
</tr>
<tr>
<td>Treatment of rejection</td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>C</td>
</tr>
<tr>
<td>Muromonab-CD3 (Orthoclone OKT3)</td>
<td>C</td>
</tr>
<tr>
<td>Antithymocyte globulin (Thymoglobulin)</td>
<td>C</td>
</tr>
<tr>
<td>Antithymocyte globulin, antilymphocyte globulin (ATGAM, ATG)</td>
<td>C</td>
</tr>
</tbody>
</table>

* Induction therapy is used within the first hours to weeks after transplantation to prevent initial recognition of the allograft. Maintenance therapy is used on a daily basis to prevent rejection of the graft.
† The FDA categories are defined as follows: A (not listed here) indicates that controlled human studies show no risk. B indicates that no evidence of risk in humans has been found — either studies in animals show risk whereas in human findings do not, or, if no adequate studies in humans have been done, the animal findings are negative. C indicates that human risk cannot be ruled out — studies in humans are lacking and studies in animals are either positive for risk or lacking. D indicates evidence of human risk. X (not listed) signifies that the use of the drug is contraindicated during pregnancy. Studies in animals or humans (or investigational or post-marketing reports) have demonstrated fetal risk that outweighs any potential benefit.

Structural malformations in children of transplant recipients

Registry records and case reports to date have not been able to find unifying patterns of malformations in children of recipients of solid organs. Prednisone is associated with scattered birth defects, particularly at doses exceeding 20 mg per day.44 Sporadic congenital malformations were reported in babies of women with rheumatologic diseases who were receiving azathioprine,90,99 and dose-related fetal myelosuppression90 and transient neonatal immunosuppression100 were also reported. Calcineurin inhibitors are associated with isolated birth defects in humans.101,102 Although the list of potential malformations is worrisome, their incidence remains low, and the patterns of the defects are so inconsistent that defining any of the immunosuppressive medications as a teratogen or fetotoxin is difficult. Specific patterns may not be identified because the numbers of treated patients are limited in comparison to the numbers needed for relationships to be detected or because the reported events are random occurrences. The prevalence of major structural malformations according to the National Transplantation Pregnancy Registry was approximately 4 to 5 percent,7 figures similar to the 3 percent reported in pregnant women without disease.3

Structural malformations in offspring of animals exposed to mycophenolate mofetil during pregnancy led the manufacturers to include on the label a recommendation for caution in its use during pregnancy. The use of mycophenolate mofetil has also been discouraged by the European transplantation community.41 According to a recent re-
Drug-Induced Immunologic Abnormalities in the Fetus and Newborn

There are few data about the effects of immunosuppressive agents on the immune system of the fetus and the neonate. Few preclinical studies in animal models have included the neonatal immune system as an end point, despite the fact that the immune system is a primary target of these drugs in the mother. Both cyclosporine and tacrolimus interrupt normal T-cell development and promote the survival of T cells that are able to react against normal tissue. Laboratory mice exposed to cyclosporine or tacrolimus during the third trimester of pregnancy, a critical time for the development of the immune system, have been found to have hypoplastic peripheral lymphatic organs, to lack mature T cells, and to have dysfunctional T-cell reactivity. Thus, the few rodent studies that have examined in utero exposure to immunosuppressive drugs suggest that there are profound effects on the developing immune system.

Few immunologic studies have been conducted in human neonates. One study showed that mature T cells failed to develop in infants born to women who were treated with cyclosporine. In a study of six infants exposed to immunosuppressants in utero, low numbers of B cells were observed in the peripheral blood at one and three months of age, whereas the T-cell numbers were normal. Another study of infants exposed to immunosuppressants in utero reported that the numbers of T and B cells were low at birth and normalized within a few months; the study also reported low expression of some T- and B-cell–surface molecules (CD25 and HLA-DR on T cells and CD5 on B cells) for up to a year after birth, low total IgG levels at two months of age, and low IgG1 and IgG3 levels up to six months after birth. The importance of these observations and their implications for care of the children of women who have received solid-organ transplants are unknown. Several other studies reported normal immunologic function in infants exposed to immunosuppressive drugs in utero. Whether autoimmune disease is a concern for the future has been raised by one isolated case report describing the daughter of a transplant recipient in whom joint stiffness developed at the age of 8 years, ulcerative colitis at the age of 16, and multiple autoantibodies and systemic lupus erythematosus when she became pregnant. There have been no systematic or frequent reports of autoimmune disease in the offspring of transplant recipients; therefore, whether sporadic cases of autoimmune disease are related to immunosuppressive exposure in utero is unknown. A retrospective analysis of the offspring of mothers with kidney transplants using data from the Motherisk Program in Canada reported only one child with insulin-dependent diabetes mellitus and two children with asthma; the rates of these disorders do not appear to differ from the expected rates among the general population.

LONG-TERM CONSEQUENCES OF IN UTERO EXPOSURE TO IMMUNOSUPPRESSIVE MEDICATIONS

The long-term consequences of in utero exposure to immunosuppressive agents are unknown. No structural or developmental abnormalities were noted in 48 children of recipients of solid organs who were followed for a mean of 5.2 years, even though the prematurity rate among these children was 56 percent. The National Transplantation Pregnancy Registry reported a 4 percent prevalence of major structural malformations in 164 children born to mothers with solid-organ transplants, but long-term follow-up of the children was not described. In another National Transplantation Pregnancy Registry study, 175 children born to mothers who took cyclosporine during gestation were followed. Seventy-one of the children were of school age (5 through 12 years). Data obtained from telephone interviews indicated that 17 of these children (24 percent) had developmental delays. Since prospective neurocognitive testing is not routinely recommended for children born to mothers with solid-organ transplants, the neurocognitive follow-up data are extremely limited.

Registry data underscore the occurrence of complications such as fetal growth retardation,
preeclampsia, and premature birth, all of which are risk factors for neurocognitive impairment.\textsuperscript{120,121} The Motherisk Program reported that among 32 children born to mothers with solid-organ transplants, 1 had a sensorineural hearing loss, 1 had a learning disability, and another had a pervasive developmental disorder.\textsuperscript{113} There were no typical precipitating causes, such as perinatal asphyxia, in these three children.\textsuperscript{113} There are other reports of sensorineural hearing loss and learning disabilities in children of transplant recipients, but the numbers are small.\textsuperscript{3,119} In general, learning disabilities are not detected until children enter school, and even then, specific learning disabilities may not be adequately identified.\textsuperscript{122} Data based on careful neurocognitive testing and long-term pediatric follow-up are lacking for children born to women with solid-organ transplants.

**BREAST-FEEDING BY MOTHERS RECEIVING IMMUNOSUPPRESSIVE MEDICATION**

Few data are available on breast-feeding by mothers taking immunosuppressive medication. The American Association of Pediatrics supports breast-feeding by mothers taking prednisone, advises against breast-feeding by those taking cyclosporine, and provides no recommendations regarding azathioprine or tacrolimus.\textsuperscript{123,124} The current literature regarding immunosuppressive-drug levels in breast milk is confusing, since the levels vary from undetectable to therapeutic or equal to those in maternal serum.\textsuperscript{80,84} There are no data on the levels of mycophenolate mofetil or sirolimus (formerly known as rapamycin) in breast milk in humans. Whether the risks of exposure to immunosuppression through breast milk outweigh the benefits of breast-feeding remains unknown.

**CONCLUSIONS**

Even as progress occurs in the medical and surgical management of pregnancy in recipients of solid-organ transplants, health care professionals and transplant recipients should consider the potential risks of pregnancy as well as the risks for the offspring. Now that successful short-term outcomes have been reported, the transplantation community will be able to focus on the long-term consequences for both mother and child. Physicians should be strongly encouraged to report both favorable and unfavorable pregnancy outcomes to existing registries. The current state of knowledge makes it difficult to quantify the risks of pregnancy for transplant recipients, just as it is difficult to quantify the risks for older women or for those with diabetes who are considering pregnancy. We must inform our patients about what we know and what we do not yet know and provide optimal care as our patients embark on this other “gift of life,” bearing a child.

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