Safety considerations: breastfeeding after transplant

Organ transplant is an effective treatment for end-stage organ failure. For women, restoration of organ function can restore fertility and the ability to successfully carry a pregnancy. Posttransplant pregnancies have been reported among recipients of all types of solid organ transplants via case and center reports plus registry data. Stable graft function is dependent on prevention of rejection, currently accomplished by using maintenance immunosuppressant medications, to which the fetus is exposed in utero. Common among neonatal outcomes in transplant recipients are preterm and low-birth-weight infants. Emotional, nutritional, and immunologic benefits of breastfeeding have been well-documented and could be valuable for these newborns. Concern must be directed at the effects of the child's exposure to immunosuppressive agents excreted into the breast milk. Breastfeeding could be considered in transplant recipients if it can be shown that the level of exposure does not result in risks to the newborn, immediately and throughout childhood. Despite concerns of health care professionals, some recipients have chosen to breastfeed. Breastfeeding after transplant must be approached with consideration of many issues, and the potential risks require further study. This review focuses on benefits of breastfeeding, common immunosuppressive agents used in organ transplant recipients, a summary of the reports of women who have breastfed their infants while on immunosuppressive therapy and the published studies on breastfeeding and immunosuppressive agents. Recommendations are provided to guide health care professionals to help mothers receiving immunosuppressive agents to make informed choices about breastfeeding their infants. (*Progress in Transplantation.* 2013;23:137-146)

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According to the American Academy of Pediatrics (AAP), breast milk is the superior form of nutrition for an infant through the first 12 months, especially for preterm and low-birth-weight (LBW) infants.[1] The immunological benefits of breastfeeding are well-documented.[2,3] Physiological benefits of breastfeeding over bottle feeding (formula) include a decreased risk of necrotizing enterocolitis, greater enteral feed tolerance, lower risk of infection, higher oxygen saturation levels, improved retinal function, improved cognitive performance, and a reduced risk of allergies developing later in life.[2,4-12] After being exclusively breastfed for the first 6 months of life, term infants who were either small or appropriate for gestational age scored a mean of 3 to 11 points higher on intelligence tests at 5 years of age than did infants fed formula or solids during this period.[13]

In the past 2 decades, the benefits of breastfeeding LBW and preterm infants have been demonstrated in controlled clinical trials in the general population (reviewed by Meier and Brown[2]).[14,15] As preterm delivery and LBW occur in more than 50% of live births in female transplant recipients, breastfeeding or administering human milk to these infants could be an effective therapeutic intervention to support growth and well-being in this population were it proven to be risk-free. However, breastfeeding by mothers on immunosuppressive therapy has been discouraged as these agents are excreted in colostrum and breast milk.[16-18]

Breast Milk Composition

The composition of human milk varies according to the phase in which it is secreted: colostrum, transitional milk, and mature milk in sequence. The first milk, colostrum, has the highest concentration of immunoglobulins and a higher protein content than mature milk. Colostrum is produced prepartum through days 1 to 5 postpartum. Colostrum contains approximately 58 Kcal/dL; mature milk contains 70 Kcal/dL. Transitional milk can appear as early as 12 hours after delivery and continue for 7 to 14 days. The concentrations of immunoglobulins, protein, and total calories decrease in transitional milk but concentrations of lactose and fat increase. Mature milk appears as early as 3 days postpartum, becomes predominant by day 9, and has a lower concentration of immune factors than colostrum has.

Breast milk is considered an immune promoter that not only nourishes, but also protects and enhances growth and development of the infant's gastrointestinal tract.[6] Secretory IgA is the primary antibody found in human milk. Other immunoglobulins (IgG, IgM, and IgE) are found in small amounts and decrease significantly over time. Cells found in colostrum and breast milk are predominantly macrophages, but also include polymorphonuclear leukocytes and lymphocytes.[14,19-21] Putative effects of milk cytokines include stimulation of host defenses, prevention of autoimmunity, anti-inflammatory effects in the upper respiratory and gastrointestinal tracts, and stimulation of the development of the mucosal immune system of the gastrointestinal tract. Milk prolactin acts as a developmental regulator of the neonatal immune system, supporting the premise that breast milk constituents may serve as neonatal immunodevelopment agents.[19-22]

To be active in the gastrointestinal tract, proteins must be able to resist proteolytic degradation.[23-28] Although most proteins in breast milk are digested, in vitro studies have shown that the human milk proteins lactoferrin, haptocorrin, α_1-antitrypsin, and transforming growth factor-β are resistant to proteolysis and can remain intact or as larger fragments as they pass through the gastrointestinal tract. This capacity is most likely due to the structure of these molecules, which renders them resistant to proteolysis, and to the fact that conditions for effective protein digestion are not fully developed.[24,26,29] Gastric pH in young infants is typically between 3 and 5, which impairs gastric enzymes, and reaches lower levels of 1 to 2 in the next 2 years as gastric acid secretion increases.[23,30,31] The intestinal concentration of pancreatic lipases and bile salts is lower at birth than later in life.[29-31] Thus, some ingested proteins are able to remain intact as they pass through at least part of the gastrointestinal tract.

Maintenance Immunosuppressive Agents Approved by the Food and Drug Administration

Beginning in 1962, azathioprine and corticosteroids were the original cornerstones of posttransplant maintenance immunosuppression. Cyclosporine was introduced in the early 1980s, followed by cyclosporine modified USP, tacrolimus, mycophenolate mofetil, sirolimus, enteric-coated mycophenolate sodium, everolimus, and belatacept. Table 1 presents maintenance immunosuppressive agents approved by the Food and Drug Administration.

Corticosteroids

Corticosteroids have broad anti-inflammatory and immunosuppressive properties, including decreased proinflammatory cytokine production as well as induction of genes that inhibit cyclooxygenase-2, adhesion molecules, and other inflammatory mediators.[32] Most corticosteroids, with the exception of betamethasone and dexamethasone, are metabolized in the placenta by 11-β-hydrogenase to inactivated forms, leaving less than 10% of the active drug to reach the fetus.[33]

Although glucocorticoid exposure during pregnancy does not represent a major teratogenic risk in humans at therapeutic doses, it has been reported to increase by 3.4-fold the risk of cleft lip and palate, consistent with findings from animal studies.[34-36] Rare cases of transient fetal adrenal suppression have been reported, suggesting that exposed infants should be closely monitored. Only small amounts of corticosteroids are present in breast milk, at most 0.1% of the total prednisolone ingested by the mother—which is less than 10% of an infant's endogenous corticosteroid production.[37] Breastfeeding in the presence of corticosteroids is considered safe by the American Academy of Pediatrics (AAP).[1]

Calcineurin Inhibitors: Cyclosporine and Tacrolimus

Calcineurin inhibitors exert their effects on helper T-cells via inhibition of the calcineurin-dependent signal transduction pathway between cell surface receptors and nuclear transcription events. This pathway is responsible for antigen-specific T-cell activation.[38]

Table 1 Food and Drug Administration's pregnancy categories for immunosuppressive drugs commonly used in transplant[3]

Drug	Pregnancy category[a]
Corticosteroids (prednisone, prednisolone, methylprednisolone)	B or C
Azathioprine (Imuran)	D
Cyclosporine (Sandimmune)	C
Cyclosporine modified (Neoral)	C
Tacrolimus (Prograf)	C
Mycophenolate mofetil (Cellcept)	D
Enteric-coated mycophenolate sodium (Myfortic)	D
Sirolimus (Rapamune)	C
Belatacept (Nulojix)	C
Antithymocyte globulin (Atgam, ATG)	C
Antithymocyte globulin (Thymoglobulin)	C
Muromonab-CD3 (OKT3)	C
Basiliximab (Simulect)	B
Daclizumab (Zenapax)	C

[a] Categories briefly defined: B = no fetal risk, no controlled studies; C = fetal risk cannot be ruled out; D = evidence of fetal risk.

Cyclosporine and tacrolimus are excreted in breast milk.[16,17] In a recent study,[39] blood levels of tacrolimus in breast milk–fed infants of women using the drug during pregnancy and lactation were undetectable 14 days postpartum. Assuming a maternal tacrolimus dose of 6 mg per day and breast milk ingestion of 0.15 L/kg per day, those researchers estimated the infant dose to be 0.78 μg/d, equivalent to 0.32% of the maternal dose (based on highest breast milk concentration 2.1 μg/L).[39] In 1994, the AAP[1] opined that breastfeeding by cyclosporine-treated mothers was contraindicated. This was modified in a 2001 consensus statement to "not recommended." More recently, the AAP has moved cyclosporine to a new category designation, "Cytotoxic Drugs That May Interfere With Cellular Metabolism of the Nursing Infant."[1] Note that neither calcineurin inhibitor is cytotoxic, that is, causes cell death.

Azathioprine and Mycophenolic Acid Derivatives

Azathioprine and mycophenolic acid (MPA) derivatives are antimetabolites that block DNA synthesis by interfering with purine metabolism,[40] thereby inhibiting lymphocyte proliferation and clonal expansion. Azathioprine is a prodrug that is converted to 6-mercaptopurine, a purine analog that interferes with nucleotide synthesis. Its most common adverse effect is bone marrow suppression. From 1962 until the early 1980s, in combination with corticosteroids, azathioprine was the standard for clinical immunosuppression. In a study[41] investigating levels of the metabolically active breakdown product of azathioprine, 6-mercaptopurine, in breast milk from women receiving azathioprine during pregnancy, researchers reported that 6-mercaptopurine was infrequently detectable in breast milk. 6-Mercaptopurine was detected in 1 of 30 breast milk samples 28 days postpartum at concentrations of 1.2 and 7.6 μg/L at 3 and 6 hours after administration of azathioprine, respectively. The 29 other samples assessed did not yield detectable levels of 6-mercaptopurine.[41] With the introduction of cyclosporine, azathioprine became an adjunctive drug used at much lower doses, and it has been largely supplanted by the MPA derivatives.

MPA is a potent antimetabolite that reversibly inhibits the enzyme inosine monophosphate dehydrogenase, a rate-limiting enzyme in the de novo purine synthesis pathway on which lymphocytes are dependent.[42] When used in combination with a calcineurin inhibitor and corticosteroids, MPA is more effective than azathioprine in preventing acute rejection. It is not known whether MPA passes into breast milk. Data on breastfeeding while being treated with MPA are currently very limited.

mTOR Inhibitors

Sirolimus and everolimus inhibit the mammalian target of rapamycin (mTOR) protein kinases, which prevent T-cell cycle progression by blocking the ability of T-cells to proliferate in response to interleukin 2 stimulation. Aside from immunosuppressive properties, these drugs possess antiproliferative effects. The impact of these effects on fetal and early childhood development is unknown.[43] No data are available on the excretion of these compounds in breast milk.

Belatacept

Belatacept is a selective T-cell costimulation blocker recently approved (in 2011) for prophylaxis of organ rejection in adult kidney transplant recipients. Unlike the other agents discussed, belatacept is a "large" molecule (molecular weight, 91.5 kDa) administered only intravenously. No pregnancy outcomes have been reported with exposure to belatacept.[44]

In Utero Exposure to Immunosuppressive Therapy

Many immunosuppressants are transferred across the placenta.[45-49] Thus, in utero exposure to immunosuppressives may affect an infant's immune system. In this section, we review in utero exposure to immunosuppressive medications administered to pregnant transplant recipients and pregnant women receiving immunosuppressants for other conditions.

Researchers in several studies have reported that infants exposed in utero to cyclosporine are born with lower levels of B cells and impaired T, B, and NK-cell development and/or maturation. These effects are still apparent at 1 year of age.[47-49] Di Paolo et al[47] studied 6 nonbreastfed infants born to mothers treated with cyclosporine and found that the infants' peripheral B-cells, total T-cells, as well as CD4+ and CD8+ T-cells returned to the normal range after the first year of life. Total IgG concentration was significantly lower than that of control infants at 2 months of age, with subnormal levels of IgG1 and IgG3 subclasses, and remained low up to 6 months of age. These infants showed normal numbers of natural killer cells, whereas the expression of CD57+ cells (non–MHC-restricted cytotoxic lymphocytes) were barely detectable at birth and failed to increase over time in both CD8+ and CD8- subsets. Di Paolo et al[47] reported no clinical evidence of an immunodeficient state. The authors suggested that it may be prudent to delay conventional vaccinations until after the first year of life.

Baarsma and Kamps[48] studied immunological responses during the first 2 years of life of an infant born to a liver transplant recipient who took cyclosporine during her pregnancy. Shortly after birth, lymphocyte subsets were low in the infant, particularly B lymphocytes. The distribution of lymphocytes returned to low normal ranges within the first 2 years of life except for CD8 cells, which remained low. No other signs of persisting effects of cyclosporine on the functional integrity of the immune system were seen. Those investigators[48] reported that the infant demonstrated a normal IgG-antibody response to routine vaccinations (diphtheria-tetanus-pertussis and inactivated poliomyelitis) at 4, 5, and 6 months of age.

Takahashi et al[49] investigated the lymphocyte subpopulations and T-cell subsets in the blood of 6 newborn infants from mothers receiving cyclosporine, azathioprine, and prednisone. Cord blood and then peripheral blood were obtained from the infants at 1 month and 3 months of age. Control samples were obtained from 5 nonexposed newborns. Takahashi et al reported that the number of B cells was significantly lower in subjects than controls but that there were no significant differences between numbers of CD2+, CD4+, or CD8+ cells. B-cell counts remained low at 1 and 3 months of life. These authors concluded that it was possible that B-cell lines were more sensitive to in utero exposure to immunosuppressants than were T-cell lines.[49]

Azathioprine is clastogenic, meaning it can induce disruption or breakage in chromosomes. Newborns of kidney transplant recipients, who had been exposed to azathioprine in utero, had abnormal chromosomes in circulating mononuclear cells early postpartum, although these were no longer detectable at 3 months of age. In a cohort study focusing on azathioprine influences on teratogenesis, 189 women taking azathioprine for a variety of conditions throughout pregnancy were compared with 230 controls not taking azathioprine.[50] The rate of major malformations did not significantly differ between groups, with a rate of 3.5% in those taking azathioprine versus 3.0% in controls. The azathioprine group had more cases of preterm delivery and a lower mean birth weight for gestational age than did controls. The indications for taking azathioprine were not stated. Patients undergoing treatment for autoimmune disease may not be the same as transplant recipients in terms of drug bioavailability and metabolism. Outcome and follow-up studies of children born to recipients reported to the National Transplantation Pregnancy Registry (NTPR) have not measured immune responsiveness, but no gross immune defects have been reported.[51,52]

In a case study[53] examining the effect of intrauterine exposure to azathioprine during the pregnancies of 3 patients with autoimmune disease, researchers found evidence to suggest that the placenta forms a relative barrier to azathioprine and its metabolites. 6-Thioguanine nucleotides (6-TGNs) are the active form of 6-mercaptopurine, whereas 6-methyl mercaptopurine (6-MMP) is a potentially hepatotoxic byproduct of azathioprine. No 6-MMP could be detected in the 3 infants in the study, whereas 6-TGN was present in the red blood cells of the newborns, albeit at a lower concentration than in the mothers. The investigators concluded that the placenta is impenetrable to 6-MMP but does allow some passage of 6-TGN. The outcomes of the pregnancies were successful, with no evidence of teratogenicity or any other health complications.

In a recent study, Cleary and Källén[54] investigated the pregnancy outcomes of 476 women who used azathioprine for inflammatory bowel disease and other autoimmune diseases during early pregnancy. Using data gathered from the Swedish Medical Registry, the

authors found that the rate of congenital malformations was 6.2% in the azathioprine group and 4.7% among all infants born in Sweden. An association between azathioprine exposure in early pregnancy and ventricular/atrial septal defects was found. The researchers also reported that exposed infants were more likely to be preterm and/or small for gestational age.[54]

MPA is classified by the Food and Drug Administration as category D, because studies in pregnant women have shown that it presents a risk to the fetus.[55-63] Before the use of MPA, the incidence of birth defects in the newborns of transplant recipients appeared to be in the range of 4% to 5%.[64] An NTPR analysis included 68 (44 kidney, 5 pancreas-kidney, 9 liver, and 10 heart) transplant recipients who have reported 97 pregnancies (98 outcomes, includes 1 set of twins) with exposure to MPA products (n = 95 MMF; n = 2 enteric-coated mycophenolate sodium [EC-MPS]). Maternal dosage varied greatly from 250 mg daily to 1500 mg twice a day (MMF) and from 180 mg to 720 mg twice a day (EC-MPS). Pregnancy outcomes included 48 livebirths (49%), 48 spontaneous abortions (49%), and 2 stillbirths (2%), indicating a higher incidence of spontaneous abortion. Multiple anomalies were reported in 1 stillbirth. Structural birth defects were described in 11 of the 48 live births, an incidence of 23%. Birth defects included hypoplastic nails and shortened fifth fingers (n = 1), cleft lip and palate and microtia (n = 1), microtia (n = 1), syndactyly and ear malformations (n = 1), facial malformations (n = 1), duodenal atresia, atrioventricular canal defect, and tetralogy of Fallot (n = 1), total anomalous pulmonary venous return (n = 1). Four infants had multiple anomalies and died.[64]

NTPR Data: Breastfeeding and Outcomes for Children

The NTPR was established in the United States in 1991 to study the safety of pregnancy in female transplant recipients as well as outcomes of pregnancies where the father was a transplant recipient. Pregnancies reported to the NTPR as of December 2011 are shown in Table 2. Although the outcomes differ for each type of organ recipient group, a high incidence of preterm delivery and LBW has been seen consistently among the newborns.[64] Other reports in the literature are consistent with these findings.[65,66]

Table 3 shows data for those recipients known to the NTPR to have breastfed after receiving a transplant (some published previously).[64,67,68] In the NTPR database, 11 female kidney recipients breastfed 12 children while being treated with cyclosporine for periods ranging from a few days to 8 months. Gestational age and birth weight ranged from 32 to 40 weeks and from 1814 to 3260 g, respectively. One recipient stopped breastfeeding after 2 weeks when breast milk analysis revealed detectable cyclosporine.

Table 2 National Transplantation Pregnancy Registry: pregnancies in female transplant recipients

Organ	Recipients	Pregnancies	Outcomes[a]
Kidney	922	1490	1525
Liver	179	319	325
Liver-kidney	5	7	8
Small-bowel	2	2	2
Pancreas-kidney	50	90	95
Pancreas alone	2	5	6
Heart	60	105	109
Heart-lung	5	5	5
Lung	22	31	33
Totals	1247	2054	2108

[a] Includes twins, triplets, and quadruplets, as of December 2011.

This child was reported healthy at age 4.5 years. No problems associated with breastfeeding were reported among the 12 children with follow-up from 1.1 to 22.2 years of age.

Twenty-one kidney recipients reported breastfeeding 26 children for periods ranging from 1 week to 2 years while being treated with cyclosporine modified USP. The 26 children ranged in gestational age from 31 to 40.5 weeks, with birth weights ranging from 2540 to 3459 g. No problems associated with breastfeeding were reported among the 22 children, with a follow-up from 4 months to 13.5 years of age.

Thirty-four kidney recipients taking tacrolimus breastfed their 37 children for periods ranging from 1 week to 1.5 years. Gestational age ranged from 24 to 41 weeks, with birth weights from 539 to 3912 g. No problems associated with breastfeeding were reported among the 30 children, with follow-up from 3 weeks to 9.4 years of age.

In the NTPR liver database, 23 women breastfed 29 infants (3 infants exposed to cyclosporine, 4 to cyclosporine modified USP, and 22 to tacrolimus). These 30 children ranged in gestational age from 26 to 41 weeks with birth weights from 680 to 4097 g. Four children were breastfed briefly (2 weeks or less). One recipient breastfed 2 consecutive children for 6 months while taking cyclosporine and 8 months while taking cyclosporine-modified USP. The children were reported healthy and developing well at ages 9.5 and 13.5 years. The first child was tested for cyclosporine levels, which were undetectable as reported by the mother; the second child was not tested. Another child who was breastfed for 4 months had a mildly elevated platelet count and an abnormal albumin/globulin ratio for age; at 16 months, laboratory values were normal. At last follow-up, the child was reported healthy and developing normally at age 5 years. No additional

Table 3 National Transplantation Pregnancy Registry: breastfeeding among transplant recipients by organ and calcineurin inhibitor

Transplanted organ/regimen	No. of recipients/children	Gestational age, weeks	Birth weight, g	Length of time breast-fed
Kidney/cyclosporine	11/ 12	32-40	1814-3260	Few days-8 months
Kidney/cyclosporine modified	21/26	31-40.5	1503-3459	1 week-2 years
Kidney/tacrolimus	34/45	24-41	539-3912	1 week-1.5 year
Liver/cyclosporine (3), cyclosporine modified (4), tacrolimus (22)	23/29	26-41	680-4097	<2 weeks-1.5 years
Liver-kidney (tacrolimus)	1 / 1	37	2792	4 months
Pancreas-kidney cyclosporine modified (2), tacrolimus (3)	4/5	34-35	1814-2580	6 weeks (with 1-2 supplemental feedings)-2 years
Lung/cyclosporine (1), tacrolimus (2)	3/3	34-37	1899-2367	10 weeks and 3 months
Heart/all tacrolimus	6/10	34-40	1758-2858	5 weeks-14 months
Heart-lung/cyclosporine	1/1	36.5	2013	1 month

adverse events due to breastfeeding have been reported in these children, with follow-up from ages 3 weeks to 15.8 years old. One liver-kidney recipient breastfed her infant for 4 months while on a tacrolimus-based regimen. The child was healthy at age 6.7 years with no reported problems related to breastfeeding.

One pancreas-kidney recipient being treated with cyclosporine breastfed 2 successive children for 2 years each with no reported problems.[68] Three recipients taking tacrolimus breastfed for 6 weeks to 2 years. Gestational age and birth weights ranged from 34 to 35 weeks and from 1814 to 2580 g. No problems associated with breastfeeding had been reported in the children at last follow-up at ages 5 months to 12.8 years.

Six heart recipients being treated with tacrolimus reported breastfeeding their 10 infants for 5 weeks to 14 months. Gestational age and birth weights ranged from 34 to 40 weeks and from 1758 to 2858 g, respectively. No problems were reported in these children 1.4 to 11.2 years later.

Three lung recipients, 1 taking cyclosporine and 2 taking tacrolimus, breastfed their 3 infants. Gestational ages were 34 to 37 weeks and birth weights were 1899 to 2367 g. No problems associated with breastfeeding were reported in the children at last follow-up, ages 6.3 and 5.7 years. A heart-lung recipient breastfed her infant for 1 month while taking cyclosporine. The infant was born at 36.5 weeks and weighed 2013 g. The child was reported healthy and developing well at age 10 years.

Breastfeeding During Immunosuppressive Therapy: Literature Review

The review was conducted on MEDLINE (from 1966 to 2009), Embase (from 1988 to 1999), and PubMed (from 2005 to 2011). The following search terms were used: cyclosporine, tacrolimus, prednisone, azathioprine, mycophenolate mofetil, sirolimus, breast milk, breastfeeding, lactation, pregnancy, immunosuppressive agents, organ transplantation, and reproductive health.[16-18,35,36,41,67-79]

Gardiner et al[69] measured the concentrations of 6-TGN and 6-MMP in the blood of 4 breastfed infants while their mothers were taking azathioprine and compared these with maternal concentrations at 3 months postpartum. Maternal concentrations of 6-TGN and 6-MMP nucleotides were consistent with therapeutic levels, but neither 6-TGN nor 6-MMP nucleotides was detected in the exposed infants. The authors suggest that breastfeeding while taking azathioprine may be considered "safe."

A 2006 report provided data on 4 patients taking azathioprine while lactating.[70] In 2 patients, the excretion of azathioprine and 6-mercaptopurine into breast milk was measured and both were undetectable. Sau et al[41] measured the concentration of 6-mercaptopurine in breast milk of mothers receiving azathioprine and of 6-TGN in the blood of their babies. Ten women provided 31 samples of breast milk. 6-Mercaptopurine was detected in 2 samples from the same woman but was undetectable in the other 29 samples. No 6-TGN was detected in the blood of the 10 infants. The authors concluded that breastfeeding should not be contraindicated for infants of mothers receiving azathioprine.

In a 2008 study, 6-mercaptopurine concentrations in maternal milk and plasma were quantified.[71] Milk and plasma samples were obtained from 8 lactating women for 5 successive hours after administration of azathioprine. Plasma concentrations reached peak values ranging from 2 to 50 μg/L within 1 hour. Most of the 6-mercaptopurine excreted in breast milk was excreted within the first 4 hours after ingestion of the

drug. The authors noted that in a worst-case scenario, using the highest 6-mercaptopurine concentration found in the milk samples adjusted to the amount fed to an infant in a 24-hour period, the infant would receive 0.0075 mg/kg body weight, less than 1% of the maternal dose and 1/1000th of the therapeutic dose of 1 mg/kg. The authors concluded that breastfeeding while being treated with azathioprine appears safe.[71]

Several reports on the absorption of cyclosporine in breastfed infants have been published. Flechner et al[18] reported in 1985 that cyclosporine was present in amniotic fluid, cord blood, placental tissues, and breast milk at levels similar to the maternal serum levels of cyclosporine. Cord blood and maternal serum displayed 25% and 33% suppression, respectively, of a third-party mixed lymphocyte culture compared with controls. This study showed that cyclosporine was present and did have the potential to produce immunosuppressive effects in the fetus. In 1998, Nyberg et al[72] reported cyclosporine levels in the whole blood of 7 kidney recipient mothers and their infants and in breast milk. Although maternal blood cyclosporine levels ranged from 55 to 130 µg/L (12-hour trough), and 50 to 227 µg/L in breast milk (mean for each woman), none of the 7 infants had detectable cyclosporine in their blood. It was estimated that the infants' cyclosporine exposure was less than 0.1 mg/kg per day (therapeutic starting doses are in the accepted usage range of 4-6 mg/kg per day in divided doses). Serum creatinine was measured in infants 1 week after birth and after 4 to 12 months of breastfeeding. At the end of the follow-up, all infants had a normal serum level of creatinine, and all infants thrived and developed normally. The investigators concluded that breastfed infants of mothers treated with cyclosporine showed no signs of renal impairment and absorbed undetectable amounts of cyclosporine.[72]

In the following case studies, infants breastfed by their cyclosporine-treated mothers did not have detectable cyclosporine in their blood. Thiru et al[73] tested 1 infant's blood at age 5 weeks and found the cyclosporine level to be undetectable. Based on this level, and the mother's cyclosporine dose and milk cyclosporine concentration, the authors postulated that an infant taking 150 mL/kg of breast milk daily would receive less than 0.1mg/kg per day of cyclosporine. Behrens et al[17] calculated the potential amount of cyclosporine consumed by an infant who was breastfed by using the following calculations: assuming a daily breast milk consumption of 600 mL/day in the first month, and the cyclosporine concentration in breast milk to be 300 µg/L, then 0.06 mg/kg per day of cyclosporine would be ingested by the infant, which is less than 5% of the immunosuppressive dose.

In another case study, researchers examined a male infant born at 34 weeks of gestation who weighed 1800 g.[68] His mother had received a kidney-pancreas transplant 13 months before she became pregnant and had been maintained on cyclosporine. The infant was exclusively breastfed for the first 6 months of life. The investigators measured cyclosporine concentrations in maternal blood, infant blood, and breast milk 5 times during the first 10 months of the infant's life. At each time point, the cyclosporine was undetectable in the infant's blood (<25 µg/L). The infant thrived, reaching the 55th percentile for growth and development by 12 months of age.

Morton[74] reported 2 cases of kidney transplant recipients treated with cyclosporine who breastfed their 2 infants. In the first case, the infant had an undetectable cyclosporine level 1 week postpartum, and the maternal serum trough level was 68 µg/L. In the second case, the infant had an undetectable cyclosporine level (<15 µg/L) 2 weeks postpartum, and the maternal serum level was 39 µg/L. They concluded that additional information is needed regarding breastfeeding while taking immunosuppressants.[74]

A 2003 report described the levels of cyclosporine in 4 breastfed infants.[76] One infant was estimated to have received about 1% of the maternal dose of cyclosporine. On 2 different occasions 1 month postpartum, the infant's blood had detectable cyclosporine levels (117 µg/L and 131 µg/L) that were 50% and 78% of the corresponding maternal trough blood level. The mother was advised to discontinue breastfeeding and she complied. By 18 months, the child's growth and development appeared uneventful. In the other 3 infants who were breastfed by mothers receiving cyclosporine, 2 had cyclosporine levels below the detection limit of 25 µg/L, and 1 infant did not have levels measured because of the low level of cyclosporine measured in the breast milk samples collected.

Fewer studies have involved measurement of tacrolimus levels in breast milk. Jain et al[79] analyzed the concentration of tacrolimus in 10 samples of colostrum from 6 liver transplant recipients. Tacrolimus concentrations in the colostrum ranged from 0.3 to 0.0019 µg/L. None of the mothers chose to breastfeed.

In 2003, French et al[16] published an investigation of tacrolimus in breast milk based on a single liver transplant recipient mother who began breastfeeding her infant 1 day postpartum. Manually expressed milk samples were collected for 12 hours after the morning dose of tacrolimus. Breast milk concentrations and maternal blood concentrations were determined 2 weeks postpartum. Peak breast milk concentrations of 0.57 µg/L were observed 1 hour after the dose was administered. The average breast milk concentration was 0.429 µg/L. Maternal blood concentrations of tacrolimus were 6.5 and 6.6 µg/L at 0 and 1 hour after administration, respectively. The authors concluded that an exclusively breastfed infant would, at most,

ingest 0.06 mg/kg a day or 0.06% of his or her mother's weight-adjusted dose. Using the highest range of bioavailability, the infant could maximally absorb 0.02% of the mother's weight-adjusted dose. The investigators reported that the infant at 2.5 months of age was developing well physically and neurologically.[16]

Gardiner and Begg[77] studied the milk to blood ratio for tacrolimus in the offspring of a kidney transplant recipient. The milk-to-blood ratio was 0.23, and the average tacrolimus concentration in milk was 1.8 μg/L. Other characteristics noted were a relatively flat concentration-time profile of tacrolimus in milk, a peak milk concentration of 2.1 μg/L at 4 and 8.5 hours after the dose, and a more than 6-fold higher peak plasma concentration of 13.1 μg/L at 1 hour after the dose. The authors concluded that because infants' exposure to tacrolimus in breast milk is very low, maternal tacrolimus therapy can be compatible with breastfeeding.[77] Bramham et al[39] measured the breast milk, maternal, and infant tacrolimus levels in 11 women and 12 infants. By 14 days postpartum, tacrolimus levels in the infants were undetectable. The authors calculated that the infant dose was 0.78 μg/day, which was equivalent to 0.32% of the maternal dose. The authors concluded that women taking tacrolimus should not be discouraged from breastfeeding.[39] From the published research regarding tacrolimus transfer via breast milk, the consensus is that breastfed infants are exposed to tacrolimus, but the exposure is subtherapeutic and lacks noticeable effect.

Conclusions and Recommendations

The benefits of breastfeeding, especially for preterm infants, are well documented. Colostrum and breast milk provide antibodies and other immunologically active molecules not present in formula. Although breastfeeding would appear to be an ideal intervention for the offspring of transplant recipients, immunosuppressive drugs are present in various amounts and for some drugs in unknown amounts in breast milk. The risk of exposing an infant to minimal amounts of immunosuppressive drugs via breast milk must be kept in perspective. Thus, the question is one of risk versus benefit. Do the benefits of breastfeeding an infant when the mother must take immunosuppressive agents outweigh the potential risks?

In reviewing the literature concerning breastfeeding while taking immunosuppressive agents, one author specifies 2 critical questions in determining the risk of drug-induced toxic effects among these breastfed infants: (1) how much of the drug is excreted in the breast milk and will be absorbed by the infant? and (2) at this level of exposure, what is the risk of adverse effects on the infant?[78] Ito[78] suggested that the concentration of cyclosporine in breast milk and the infant's blood should be monitored to ensure that the blood level is less than 10% of the therapeutic level. Results of several studies indicate that breastfeeding and immunosuppressive therapy may be compatible. However, in 1 study[76] of 5 infants exposed to cyclosporine via breastmilk, researchers reported that 1 infant had significant amounts of cyclosporine in her blood.

Regarding lactation, both cyclosporine and tacrolimus inhibit expression of the prolactin gene, but it is not known whether this inhibition affects colostrum and milk formation and production. Furthermore, it is not known how cyclosporine, tacrolimus, and other immunosuppressives might directly affect levels of immune factors (leukocytes, cytokines, and antibodies) in colostrum and milk. Obtaining answers to questions about the safety and effectiveness of breastfeeding by mothers treated with immunosuppressive agents is dependent on continued study. Investigators should be encouraged to measure blood levels of immunosuppressants in breastfed infants as a necessary first step in assessing safety for the infant.

Antimetabolite drugs (azathioprine, MPA derivatives) have produced mixed results in the establishment of a standard of safety for pregnant patients. In utero, azathioprine is clastogenic, but this effect appears to be transient. Azathioprine has not demonstrated significant lasting effects on the infant via breast milk. In contrast, MPA derivatives have demonstrated an increased risk of malformations from intrauterine exposure.[55-64] The potential for effects from neonatal exposure to MPA via breastfeeding remains unassessed; levels of MPA in breast milk have not been reported. For immunosuppressants whose reproductive safety and lack of fetotoxicity are still unknown, including sirolimus, everolimus and belatacept, breastfeeding risks are not known.

Little information is available that health care professionals can use to confidently recommend breastfeeding for these mothers. From this review of the literature, a health care professional should take a 3-pronged approach when assessing whether a mother receiving immunosuppressive therapy should breastfeed. First, if the mother is taking drugs of known toxicity without a safety threshold, such as MPA drugs, then the mother should probably be advised not to breastfeed. Second, if the mother is taking drugs that appear to be safe at low or unmeasurable levels, such as cyclosporine or tacrolimus, or are thought to be safe, such as corticosteroids and azathioprine, then the infant's serum should be monitored for measurable drug levels after the first week or 2 of breastfeeding, which will reflect the infant's potential exposure from ingestion of mature milk rather than in utero exposure or levels from colostrum. If significant levels of immunosuppressants are found in the infant's blood, it should probably be recommended that the mother cease breastfeeding, as the threshold for determining

a safe level of exposure to an immunosuppressive agent is not presently known. Third, for drugs of unknown safety, such as sirolimus, everolimus, and belatacept, caution must be advised.

Future studies are needed to clarify the interrelationship of drug levels in breast milk, maternal blood, and infant blood. Infant blood should be assessed for any presence of immunosuppressive drugs to evaluate the potential immunosuppressant exposure. Continued study and follow-up of all breastfed offspring of transplant recipients is essential to establish safety statements regarding the impact of immunosuppressants in breast milk on newborns and their immune development.

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