INVESTIGATION OF COGNITIVE AND PHYSICAL DEVELOPMENTAL ABILITIES OF YOUNG CHILDREN EXPOSED TO TACROLIMUS AND CYCLOSPORINE IN UTERO

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By
Robyn Richmond Chotiner
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Examining Committee Members:
Frank Farley, Advisory Chair, School Psychology
Joseph DuCette, Educational Psychology
Erin Rotheram-Fuller, School Psychology
Jerry Stahler, Geography and Urban Studies
Vincent Armenti, Pathology, Anatomy & Cell Biology and Surgery, Thomas Jefferson University

ABSTRACT

Investigation of Cognitive and Physical Developmental Abilities of Young Children Exposed to Tacrolimus and Cyclosporine in Utero
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Kidney transplant recipients must take immunosuppressive medications to prevent the rejection of their transplanted kidney. If female transplant recipients become pregnant, however, very limited data are available about the effects of these medications on their exposed offspring. This study specifically reviews two of the most commonly used immunosuppressive medications prescribed to transplant recipients, cyclosporine and tacrolimus, and evaluates physical and cognitive development of the recipients' children who were exposed to these medications in utero. Participants in this study (n = 71) were female kidney transplant recipients who (a) voluntarily consented to be part of the National Transplantation Pregnancy Registry, (b) took cyclosporine or tacrolimus while pregnant, (c) had a child who is under the age of 6 years at the time of the study, and (d) were reachable via phone. Participants were asked standardized assessment questions related to their child's cognition and physical abilities from the Development Assessment of Young Children (DAYC). Standard scores from the assessment were recorded and analyzed to show that children exposed to cyclosporine or tacrolimus showed higher cognitive scores on the DAYC compared to the normative population. Children exposed to cyclosporine also showed higher physical scores compared to the normative population. Children exposed to tacrolimus did not show significant differences in physical development from the normative population. When cyclosporine

or tacrolimus are required during pregnancy, these results help provide reassurance to parents and medical care providers about the cognitive and physical development of their offspring. Practical implications for school psychologists, limitations of this research, and directions for future research were discussed.

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CHAPTER 1

INTRODUCTION

Kidney transplantation entails placing a functioning kidney from a live donor or cadaver into a patient whose kidneys have both failed. After transplantation, kidney transplant recipients must take immunosuppressive medications for the rest of their lives; the purpose of these medications is to suppress the patient's immune system in order to prevent his/her body from rejecting the new kidney. These immunosuppressive medications help prevent rejection of the transplanted kidney, or graft, and allow patients to lead longer lives (Armenti, Moritz, Cardonick, & Davison, 2002; Ciancio, Burke, Jorge, Rosen, & Miller, 2005). Immunosuppressive medications are therefore also known as antirejection medications.

In the past, many female transplant recipients wished to conceive, but there was uncertainty about the effects of the mother's antirejection medications on the fetus. These immunosuppressive medications must be taken during pregnancy and are known to cross the placenta (EBPG, 2002; Nulman et al., 2010). The unknown short-term and/or long-term effects of these medications on a fetus and subsequent child's development have continued to concern professionals in the medical field (Oliveira, Sass, Sato, Osaki, & Medina Pestana, 2007).

Since the first child born to a transplant recipient in 1958 (Murray, Reid, Harrison & Merrill, 1963), there have been many advances and changes in the immunosuppressive regimen of transplant recipients. More research has been conducted on the effects of the immunosuppressive medications on the fetuses (Armenti et al., 2002). Furthermore, safer and more effective medications that can be used to maintain graft function have been

developed over the years. Two of the most common immunosuppressive medications that are currently being prescribed by physicians are cyclosporine and tacrolimus (Josephson & McKay, 2010). Cyclosporine has been used with transplant recipients for the past 25 years (Vincenti, 2003). However, limited research has been conducted on cyclosporine's effects on the mother's pregnancy, the fetus, and the developing child. The Food and Drug Administration (FDA) approved another immunosuppressive drug, tacrolimus, for use in the United States in 1994 (Bowman & Brennan, 2008). Unfortunately, data regarding the effects of tacrolimus on the mother's pregnancy, the fetus, or child development are also limited. Moreover, it appears that data investigating the effects of tacrolimus or cyclosporine in utero on cognitive and physical development of children are scarce in the research literature.

A registry was established in 1991 to examine the outcomes of pregnancy in U.S. solid-organ transplant recipients (Armenti et al., 2002; Grimer, 2007). The National Transplantation Pregnancy Registry (NTPR), established by Vincent Armenti M.D., Ph.D, was created to study the outcomes of pregnancies among transplant recipients and follow the offsprings' development and overall health. Pregnancy outcomes, the well-being of the offspring, and continual follow-up of recipients' health and graft function are all studied by the NTPR. Moreover, the NTPR has been instrumental in the advancement of medical knowledge and increased understanding of transplant recipients and their offspring.

Female kidney transplant recipients from the NTPR database who conceived children while taking tacrolimus or cyclosporine were contacted in this study. Information provided by the recipients offered a better understanding of possible

developmental effects on their offspring from those medications. Specifically, the cognitive and physical assessments of children exposed in utero to tacrolimus were studied and compared to the assessments of those exposed in utero to cyclosporine and to the normative population. Demographic information from the NTPR database was also accessed, looking specifically at the recipient's age of conception, creatinine level during pregnancy, and concomitant medications she was on during the pregnancy.

Because transplant recipients from the NTPR database are located throughout the United States, cognitive and physical assessments of the offspring cannot be done by individual assessment but rather through parental interview. One standardized and norm-referenced assessment tool used to assess developmental levels of children through parental interview is the Developmental Assessment of Young Children (DAYC). The DAYC, developed in 1998 by Voress and Maddox, is administered to children under the age of 6 years. The DAYC measures five areas of assessment mandated by the Individuals with Educational Disabilities Act (IDEA): cognition, communication, social/emotional development, physical development, and adaptive behavior. As each section can be administered and scored independently, the DAYC was used to measure developmental abilities of children exposed to immunosuppressive medication in utero in two of the aforementioned areas: cognitive and physical development.

Statement of the Problem

The purpose of this study was to investigate developmental effects of tacrolimus or cyclosporine medication on the offspring of female kidney transplant recipients who have been treated with those immunosuppressive drugs during pregnancy. The cognitive and physical development of children between birth to the age of 6 was explored.

Research Questions

This study addressed the following research questions:

1. Are there statistically significant differences between the DAYC scores in cognitive development of children exposed in utero to tacrolimus and the DAYC normative population?
2. Are there statistically significant differences between the DAYC scores in physical development of children exposed in utero to tacrolimus and the DAYC normative data?
3. Are there statistically significant differences of the DAYC cognitive scores between the children exposed in utero to cyclosporine versus the children exposed to Tacrolimus?
4. Are there statistically significant differences of the DAYC physical scores between the children exposed in utero to cyclosporine versus the children exposed to Tacrolimus?
5. Are there statistically significant differences between the DAYC scores in cognitive development of children exposed in utero to cyclosporine and the DAYC normative data?
6. Are there statistically significant differences between the DAYC scores in physical development of children exposed in utero to cyclosporine and the DAYC normative data?

CHAPTER 2

LITERATURE REVIEW

History of Immunosuppressive Medications for Kidney Transplant Recipients

In the 1960s, when the field of kidney transplantation was relatively new, immunosuppressive regimens for transplant recipients consisted mainly of azathioprine and prednisone. Azathioprine works by inhibiting purine metabolism. It also affects T cells and antibody production. The exact mechanism for its established ability to inhibit renal graft rejection has never been fully been elucidated (Imuran, 2006). However, due to its side effects and the approval of new, more effective medications, azathioprine is no longer a first line drug in the treatment of renal transplant patients. Azathioprine is only prescribed to 0.6% of kidney transplant recipients today (Knoll, 2008).

Prednisone is a corticosteroid with broad anti-inflammatory and immunosuppressive effects. Although corticosteroids have been around for over 40 years, they are still a part of most immunosuppressive regimens. The adverse effects of long-term corticosteroid use are numerous, including diabetes mellitus, peptic ulcer disease, hypertension, osteopenia, cataracts, and aseptic necrosis of joints. Attempts continue to be made for corticosteroid withdrawal and corticosteroid avoidance when treating transplant recipients (Armenti et al., 2002; Meyer, Decker, & Baughman, 2010).

In the 1980s, cyclosporine was introduced in combination with azathioprine and prednisone or prednisone alone. Cyclosporine is a calcineurin inhibitor. Calcineurin, a protein phosphatase, plays an important role in modulating cellular responses and T cell activation (Klee & Yang, 2003). Cyclosporine showed a large improvement in the 1-year survival rate of the transplanted kidney to about 85%, higher than the previous survival

rate of 65% achieved with azathioprine and corticosteroids medication (Golshayan & Pascual, 2008). Another calcineurin inhibitor, tacrolimus, was introduced in the early 1990's (Webster, Woodroffe, Taylor, Chapman, & Craig, 2005). Due to their similar actions, tacrolimus and cyclosporine are not used together.

Both of the aforementioned calcineurin inhibitors, cyclosporine and tacrolimus, function by suppressing the transcription of cytokines IL-2, IL-3, IL-4, IL-5, interferon-gamma, tumor necrosis factor-alpha, and granulocyte-macrophage colony-stimulating factor. Cytokine genes are necessary for T-cell activation and proliferation, and calcineurin inhibitors block the transcription of these genes. They also suppress IL-2 and IL-7 receptors (Armenti et al., 2002; Gummert, Ikonen, & Morris, 1999).

The introduction of tacrolimus and cyclosporine resulted in a dramatic decrease in acute rejection rates and improvement in graft and patient survival in kidney transplant recipients compared to earlier medications (Jose, 2007; Vincenti, 2003). Both cyclosporine and tacrolimus are now firmly entrenched as part of most primary immunosuppressive regimens (Grimer, 2007).

While calcineurin inhibitors are the most commonly used immunosuppressive agents in kidney transplant recipients, tacrolimus has begun replacing cyclosporine in treatment over the past decade. In fact, according to the 2009 Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) Annual Report: Transplant Data 1999–2008, it was noted that in 2008, 86% of living donor kidney transplant recipients received tacrolimus and 8% received cyclosporine at time of discharge. This shows a dramatic change from 1996 data, when 76% of patients received cyclosporine and 13% received tacrolimus (Knoll, 2008). The reason for the

increased use of tacrolimus is due to the recent finding that compared to cyclosporine, tacrolimus-treated patients showed a substantial improvement in graft survival within the first 6 months of transplant. There was a 44% reduction in graft loss when tacrolimus was used in the treatment plan relative to other medications (Webster et al., 2005).

While kidney transplant patients treated with tacrolimus versus cyclosporine have shown improved graft survival, tacrolimus has also been associated with an increase in side effects. Specifically, there has been an increase in diabetes, neurological deficits, and gastrointestinal symptoms. Therefore, medication choice is individualized for each transplant recipient. Risks and benefits for each patient must be considered; the choice of calcineurin inhibitors is not clear cut or straightforward in each case (Webster et al., 2005).

Thus, while tacrolimus and cyclosporine are the same class of drugs, they have different toxicities. Reported adverse reactions stated on the package insert of tacrolimus medication include neurotoxicity (such as tremor, headache, seizures), gastrointestinal concerns (diarrhea, nausea, vomiting), nephrotoxicity, hyperkalemia, hypomagnesemia, hyperglycemia, anemia, hypertension, insulin-dependent posttransplant diabetes mellitus, and malignancy and lymphoproliferative disorders. Reported side effects of cyclosporine include nephrotoxicity, hyperkalemia, hyperuricemia, gingival hyperplasia, thrombocytopenia and microangiopathic hemolytic anemia, hypertension, encephalopathy, and malignancy and lymphoproliferative disorders.

While this study focused on recipients who have used cyclosporine or tacrolimus medication, it is important to discuss the other immunosuppressive medication options used in transplant recipients. Mycophenolate mofetil (MMF) was approved for use in

1995 in the United States. To a large degree, MMF has replaced azathioprine. MMF is typically used with calcineurin inhibitors and/or corticosteroids (Armenti et al., 2002). MMF belongs to the antimetabolite class of immunosuppressives. It functions by forming mycophenolic acid, which blocks *de novo* purine synthesis. This causes decreased lymphocyte proliferation and hence, a decreased rejection response in a transplant recipient (Armenti et al., 2002).

Another antirejection drug, sirolimus, was approved by the FDA in the U.S. in 1999 (Knoll, 2008). It functions by inhibiting cytokine driven T-cell proliferation, stopping the progression from the G1 to the S-phase in the cell cycle (Armenti et al., 2002). Sirolimus is often used in combination with cyclosporine and corticosteroids after transplantation.

Just 25 years ago, physicians did not have many choices when treating transplant patients. Now there are various options for physicians to individualize immunosuppression therapy and select the best medications for each transplant recipient (Vincenti, 2003). These aforementioned new and effective immunosuppressive medications have launched unprecedented advances in kidney transplantation (Vincenti, 2003).

Furthermore, advances have also been made in understanding the functions of all these medications and their effects on pregnancy. While there was once limited information about these new medications and their potential teratogenic effects, studies have been conducted to help transplant recipients and physicians make appropriate choices for fetal and maternal health. Previously, transplant recipients were advised not to conceive; today, thousands of successful pregnancy outcomes have been reported from

transplant recipients who have taken immunosuppressive medication (Armenti et al., 2002).

Immunosuppression and Pregnancy in Transplant Recipients

Because immunosuppression medications are required for kidney transplant recipients to maintain adequate graft function and maternal survival, the effects of these medications on the fetus is an important issue (Armenti et al., 2002). The U.S. FDA categorizes drugs for pregnancy safety as category A, B, C, D, or X. Category A drugs have not been shown to demonstrate a risk to the fetus in clinical trials. The aforementioned medications do not fit into this category. Category B drugs have not been shown to be a risk to the fetus in animal reproduction studies, but there are not adequate studies in pregnant women to demonstrate safety. Prednisone is an example of a category B drug. While prednisone crosses the placenta, it is considered a low teratogenic risk and relatively safe in transplanted women (Armenti et al., 2002; EBPG, 2002).

Category C drugs have shown an adverse effect on the animal fetus but not enough adequate human studies have been conducted; potential benefits may warrant use of the drug in pregnant women despite potential risks. Most of the immunosuppressive medications fall into Category C, including cyclosporine and tacrolimus (del Mar Colon & Hibbard, 2007). Cyclosporine has not been associated with teratogenicity or mutagenicity (EBPG, 2002). However, in animal studies, fetal toxicities and abnormalities were noted at higher cyclosporine levels than those used clinically (Fein, Vechoropoulos, & Nebel, 1989; Mason et al., 1985). Cyclosporine is associated with intrauterine growth retardation, premature birth, and small-for-gestational age babies.

Low birth weight has also been noted (EBPG, 2002). Tacrolimus is a more potent calcineurin inhibitor than cyclosporine. Diabetes and transient perinatal hyperkalaemia in the newborn has been noted with the use of tacrolimus (Jain et al., 1997). Compared to cyclosporine, offspring of tacrolimus kidney patients show a trend toward lower birth weights (Armenti et al., 2002). Further discussion about these calcineurin inhibitor medications will continue in the next section.

Category D drugs show positive evidence of human fetal risk but potential benefits of the drug may be warranted in pregnant women despite the risks. Whenever possible, category D drugs should be avoided in pregnant patients. Azathioprine is an example of a category D medication (Meyer et al., 2010). It crosses the placenta and has been found to be teratogenic in high doses in animal studies. At lower doses, however, no anomalies have been described in the offspring (EBPG, 2002). The use of azathioprine has decreased markedly with the availability of newer agents such as MMF (Armenti et al., 2002). However, MMF has recently been linked to specific congenital malformations and several types of anomalies in newborns. Thus, the U.S. Food and Drug Administration has changed MMF medication to a category D classification (Vento, Aytes, Ledo, Boso, & Carey, 2008). MMF medication should be withdrawn before conception (Bia et al., 2010).

Category X drugs show positive evidence of human fetal risk. Therefore, they are contraindicated during pregnancy (Uhl, Kennedy, & Kweder, 2002). Immunosuppressive medications do not belong in this category.

While pregnancy after kidney transplantation can be safe and successful (Keitel et al., 2004; Yassaee & Moshiri, 2007), there are some risks associated with pregnancy in

transplant recipients. In general, pregnant kidney transplant recipients have shown a slightly increased rate of spontaneous miscarriage in the first trimester compared to the general population (Fuchs, Wu, & Ebcioglu, 2007). Furthermore, more than half of deliveries of renal transplant recipients are born premature at less than 37 weeks gestation (del Mar Colon & Hibbard, 2007; Fuchs et al., 2007). Despite the elevated preterm birth rate, it is difficult to determine the etiology of the increased rate (Fuchs et al., 2007). Low birthweight is also an issue for the newborns of transplant recipients (del Mar Colon & Hibbard, 2007). Furthermore, intrauterine growth restriction (IUGR) is reported in 30–50% of kidney transplant patients, causing the delivery of small for gestational age infants (del Mar Colon & Hibbard, 2007; Fuchs et al., 2007). Opportunistic infections, many of which affect the fetus, are also more common in transplant recipients due to the effects of immunosuppression medication (del Mar Colon & Hibbard, 2007).

Pregnancy and Calcineurin Inhibitors: Cyclosporine and Tacrolimus

The safety of cyclosporine and tacrolimus drugs in pregnancy has not yet been endorsed by their manufacturers (Grimer, 2007). They both cross the placenta and effects of the medication could impact the offspring. Data thus far have shown minimal teratogenic risk for malformations in the offspring.

Calcineurin inhibitors are associated with an increased risk of IUGR, and growth-restricted newborns have greater morbidities than do appropriately grown infants (del Mar Colon & Hibbard, 2007). Also, the offspring of mothers taking calcineurin inhibitors during pregnancy have shown some evidence of suppressed innate immunity in their first year of life (Grimer, 2007). However, these children are not likely to be at risk of developing immunodeficiency or autoimmunity (Grimer, 2007)

Cyclosporine

While fetal toxicities and abnormalities were noted at high cyclosporine levels in animal studies, cyclosporine in humans does not show increased evidence of congenital malformations (Armenti et al., 2006). In fact, in two extensive analyses, the overall incidence and prevalence of structural malformations seen in cyclosporine-treated offspring were not found to vary greatly from the general population (Armenti et al., 2002). Grimer (2007) performed a meta-analysis on the use of cyclosporine in pregnancy; he found the prevalence of major malformation in the fetus exposed to cyclosporine to be 4.1%, which was higher than, but not significantly different from, noncalcineurin inhibitors pregnancy data. No patterns of malformations were noted.

Cyclopsorine does show a moderate risk for intrauterine growth restriction and small-for-gestational-age babies (Armenti, 2004; Armenti et al., 2002; EBPG, 2002). Josephson and McKay (2010) noted no pattern or increased risk of birth defects with cyclosporine. No predominance of problems with attention deficit hyperactivity disorder (ADHD), neurocognitive, or immune development was found either (Coscia et al., 1999; Sifontis et al., 2006). The first study to assess both long-term neurocognitive and behavioral outcomes of kidney transplant recipients' children exposed to cyclosporine in utero using standardized assessments was published in 2010 (Nulman et al., 2010). Results from the study showed there was no association between in utero exposure to cyclosporine and children's' long-term neurocognitive and behavioral development, compared to unexposed healthy children. While this study had a small cohort (39 children exposed to cyclosporine in utero were compared with 38 matched unexposed children), it provided reassuring results concerning the long-term development of

children exposed to cyclosporine in utero. It is important to note, however, that while there is much literature on the use of cyclosporine, much of the outcome data include cyclosporine used together with azathioprine and prednisone (Armenti et al., 2002).

Tacrolimus

Tacrolimus is a more potent calcineurin inhibitor than cyclosporine. Spontaneous miscarriage was seen at a higher level during the first trimester in those recipients on tacrolimus. According to the NTPR, spontaneous miscarriage in renal transplant recipients during the first trimester was seen in 12% to 19% of recipients on cyclosporine and in about 25% of women on tacrolimus.

A report of the experience with tacrolimus as the main immunosuppressive regimen in pregnant transplant recipients in Spain suggested that pregnancy with tacrolimus medication is safe and effective with close monitoring. It showed favorable pregnancy outcomes without any major effects on intrauterine growth, no anomalies, no major incidence of malformations, no need of breathing support, and no observable pharmacological side effects (Garcia-Donaire et al., 2005). However, another study showed that IUGR, prematurity, and renal function impairment in the early neonatal period has been seen in tacrolimus-treated offspring, but with spontaneous resolution seen later on (Vyas et al., 1999).

Another case showed a higher incidence of diabetes and transient perinatal hyperkalaemia in the tacrolimus-exposed newborn (Coscia et al., 2009; Jain et al., 1997). A study by Kainz, Harabacz, Cowlrick, Gadgil, & Hagiwara (2000) found that 5.6% of tacrolimus-treated offspring (4 of 71 deliveries) had evidence of a structural malformation, but no specific pattern was evident.

No current literature was found showing the relationship between tacrolimus and any developmental or cognitive problems in the offspring. Overall, the research is limited on the effects tacrolimus may have on exposed offspring of transplant recipients.

Prematurity and Low Birth Weight: Developmental Outcomes

About 12.5% of births in the United States are preterm, which encompasses all infants born before 37 weeks of gestation (Eichenwald & Stark, 2008). Preterm infants are often further categorized by their birth weight. Those infants who weigh 2500g or less are considered "low birth weight" and account for about 10% of births. Those infants who weigh 1500g or less at birth are considered "very low birth weight (VLBW)" and account for 1.5% of live births. Those who weight 1000g or less are considered "extremely low birth weight (ELBW)," requiring the highest level of neonatal intensive care, and account for less than 1% of live births (Eichenwald & Stark, 2008; Hack, 2009).

Preterm or low birth weight children, when compared with normal birth weight or full-term children, demonstrate lower cognitive function, lower academic performance, more behavioral and emotional difficulties, and increased health problems (Hack, 2009). Furthermore, chronic health problems are prevalent, including those associated with cerebral palsy, visual and hearing impairments, respiratory problems (i.e. asthma), and poor growth attainment (Hack, 2009).

While cultural, socioeconomic, maternal age, parental educational attainment, family and environmental factors play a role in the cognitive and behavioral development of preterm and full-term infants, studies show that preterm children are more susceptible to poorer educational attainment, neuromotor and sensory impairments, medical issues, and emotional and behavioral difficulties (Johnson et al., 2010). These difficulties are

seen more prominently in children who are born in the ELBW category. These aforementioned areas are discussed further below.

Cognitive impairments are the most prevalent disability seen in premature or low birth weight children. Lower intelligence quotient (IQ) scores have been documented as well as higher rates of learning disabilities (Hack, 2009; Kessenich, 2003). There is also increasing evidence of more subtle, neuropsychological impairments such as deficits in visuospatial processes, sensorimotor skills, expressive language, and attention and executive functions (Johnson et al., 2010). These children have lower academic achievement, higher rates of early intervention and special education needs, and are less likely to graduate from high school (Kessenich, 2003). It is important to clarify, however, that while ELBW and VLBW preterm children show significantly lower mean IQ scores than full-term children, the majority of low birth weight children (> 50%) have IQ scores and abilities within the normal range (Kessenich, 2003).

Behavioral problems seen among preterm children, especially those with ELBW, predominantly consist of ADHD, generalized anxiety disorder, and autism disorders (Hack et al., 2009). Difficulty with attention and concentration categorized as ADHD, inattentive type, was the most prevalent psychiatric disorder among extremely preterm children (Johnson et al., 2010) and contributes to learning difficulties. A higher incidence of self-regulatory issues and difficulties with organization and integration of sensory information were also seen (Kessenich, 2003). Emotional issues (i.e. anxiety, depression) and difficulty with social relationships with peers were also noted.

ELBW and VLBW children have more chronic health conditions, mainly due to neurosensory deficits and rates of asthma. However, despite their chronic conditions,

preterm children report similar health status and quality of life compared to full-term or normal birth children (Hack, 2009).

To summarize the developmental outcomes of premature or low birth weight children, research shows that these children show higher rates of developmental disabilities; lower cognitive (IQ) levels; higher levels of enrollment in special education; lower scores in academic achievement, executive functioning, visual-motor and visual–spatial skills, and language skills; higher rates of attention problems; higher rates of emotional problems and self-regulatory issues; and increased health concerns. Nonetheless, while premature and low birth weight children have more challenging outcomes than normal, full-term children, the majority of preterm children function within normal limits (Kessenich, 2003).

Developmental Assessment in Children

Developmental assessment is a process of collecting data to identify a child's level of developmental functioning, determine a child's strengths and weaknesses, specify a child's specific abilities and skills, identify a child for developmental risk, or help in planning a child's intervention. A variety of assessment tools and techniques have been designed to collect data on children. In the early 1900s, children and infants were tested to assess behaviors that could be used to measure intelligence and predict an IQ score. However, longitudinal studies found an inability of infant measures to predict later intelligence. In the late 1900s, advances in the study of child and infant development occurred. Assessment instruments were needed for developmental screening, educational planning, monitoring progress, and identifying strengths and weaknesses. New assessment methods included a more comprehensive approach to

measuring children with more emphasis on development within a familial and sociocultural environment. Assessment began to include structured observations of a child in his/her natural home setting, parental interviews, and observations of parent and child interactions (Wyly, 1997).

Parents or other caregivers are a significant asset in providing information about a child. Parents are a valuable source of information about their child. Including parents in the assessment of a child can help provide the examiner with additional information. Parents know the most about their child's observable skills and current level of functioning, as they spend the most time with their children. Parents have also observed their children in a variety of settings over a period of time. Parents can accurately judge their children's skills and should be encouraged to be a part of their child's assessment (Voress & Maddox, 1998; Wyly, 1997).

The DAYC is unique in its use to measure developmental abilities of children in research studies. It assesses specific areas of strengths and weaknesses. It also incorporates the knowledge from the child's parent or caregiver into its assessment.

The DAYC is a norm-referenced assessment; it compares children's individual performance with the performance of a large reference group of age-equivalent children (Wyly, 1997). The DAYC was normed on a sample of 1,269 children residing in 27 states by experienced examiners. The normative sample selection is representative of the United States as a whole with regard to geographic region, race, ethnicity, family income, gender, rural or urban residence, educational attainment of parents, and disability status (Voress & Maddox, 1998).

The DAYC is a highly reliable test. Reliability refers to the consistency and accuracy of the DAYC's test items in measuring what they are supposed to measure (Wyly, 1997). The alpha coefficients for content sampling of the subtests round to or exceed 0.90. During the test–retest method, the test–retest coefficients for the subtests were all greater than .9 and all correlations were statistically significant at the .0001 level. When tested for interscorer differences, the coefficients of the five subtests were all .99. Overall, the DAYC shows a high degree of reliability (Voress & Maddox, 1998).

The DAYC has also been found to be a valid measure of children's development. For content-description validity purposes, the DAYC was created after 20 standardized tests were analyzed, available research on developmental age-appropriateness was reviewed, and additional research data were considered. Experimental versions of the DAYC were administered, and questions were reviewed, analyzed, altered or deleted. Item discrimination occurred and the item-total-score Pearson correlation index was used to select appropriate items. Based on item discrimination statistics, any items that were shown to be too easy, too difficult, repetitive or similar, or any items that did not correlate with the area assessed were removed. An item analysis using the entire normative sample showed that the item characteristics of the final version were appropriate (Voress & Maddox, 1998).

To detect item bias, the Delta Scores approach (Jensen, 1980) was used. Delta Scores, which are linear transformations of the z scale, were used to report results as correlation coefficients. There were several groups compared to determine item bias: male/female, African American/all other races, Hispanics/all other ethnic groups, at-risk children/normally developed children, and children with disabilities/nondisabled

children. The correlation coefficients revealed that DAYC items contain little or no bias to the aforementioned groups considered (Voress & Maddox, 1998).

To determine the criterion-prediction validity of the DAYC, the DAYC was compared to the *Battelle Developmental Inventory: Screening Test* and the *Revised Gesell and Amatruda Developmental and Neurologic Examination*. Both of these tests are used to measure children's developmental abilities. The high magnitude of coefficients from comparisons of both tests to the DAYC provides evidence for the validity of the DAYC as well as the minimal to no bias in the DAYC items (Voress & Maddox, 1998).

The construct-identification validity of the DAYC was also examined. The DAYC items showed strong relations to appropriate age levels. In terms of group differentiation, there were significantly different scores between those students who were at risk or disabled compared to normal-ranged children on the DAYC, as would be expected. Intercorrelations between the subtests were analyzed, and showed that relationships between the DAYC subtests are moderately high and support the construct validity of the test (Voress & Maddox, 1998).

Factor analysis shows that the DAYC subtests loaded on a single factor; this factor measures children's development. The DAYC Quotient is a valid indicator of development (Voress & Maddox, 1998).

Lastly, the DAYC's construct validity was obtained by correlating performance on specific items with the total score made on the test. Data showed strong evidence of the DAYC's item validity. Overall, the DAYC shows strong validity and is a valid measure of development (Voress & Maddox, 1998).

Due to the time demands of the DAYC, which can consist of spending approximately 10–20 minutes per each area assessed, all five subtests could not be administered. Two subtests were selected to assess the subjects in this study: Cognitive and Physical Development subtests. Because preterm birth is associated with lower cognitive scores and many transplant recipients have children born prematurely, the participant's cognition was considered a valuable area to evaluate. Furthermore, there is documentation that medications taken during pregnancy that cross the placenta may affect the physical development of a child. For example, the immunosuppressive medication used in transplant recipients MMF has been shown to cause physical anomalies in newborns. Therefore, the area of Physical Development was considered a valuable area to evaluate. Research to date has not shown physical anomalies in children who have been exposed to cyclosporine or tacrolimus. However, premature or low-birth-weight children have shown increased risk of sensorimotor and physical difficulties (Kessenich, 2003).

Summary

Despite significant advances in the treatment of kidney transplant recipients with new, more effective medications, limited data are available regarding specific effects of these medications on the exposed offspring, particularly in terms of their physical and cognitive development. More data and research are needed about the exposure of immunosuppressive medications in utero and the impact on child development, specifically with regard to any potential relationship to developmental or cognitive problems in those children. This study specifically evaluated the physical and cognitive areas of development in children exposed to cyclosporine and tacrolimus in utero.

Performing a developmental assessment on a young child has its challenges. It is beneficial to incorporate knowledge from the child's parent or caregiver in order to provide a more accurate assessment and understanding of the child. The DAYC is a unique test that incorporates information about a child from his/her parents when measuring developmental abilities.

CHAPTER 3

METHODOLOGY

Participants and Setting

Participants

Participants in this study were female kidney transplant recipients who voluntarily consented to be part of the National Transplantation Pregnancy Registry (NTPR). The NTPR is a private registry in which the experimenter has permission to contact the recipients. As indicated in the registry data, the participants have taken either cyclosporine or tacrolimus medication during their pregnancy. The recipients' medication history, creatinine levels during pregnancy, and age of conception are also part of the registry data. Each of the participants has delivered one or more offspring that has been exposed to the aforementioned medication and is under the age of 6 years old. The participants were reachable by telephone and agreed to answer the examiner's questions about their offspring.

There were 101 children of female kidney transplant recipients in the NTPR database who took either cyclosporine or tacrolimus during their pregnancy and had a child under 6 years of age at the time of this study. Of those 101 children, 14 of their mothers were unreachable due to wrong phone numbers and/or lack of forwarding contact information, 16 of their mothers were not available by phone after three to eight attempts, and 71 of their mothers were reachable by phone, of which 23 children were exposed to cyclosporine and 48 were exposed to tacrolimus. It is important to note that each transplant recipient was on several medications after their transplant and not solely on either tacrolimus or cyclosporine exclusively. This limitation, however, is

unavoidable as the majority of transplant recipients require multiple medication regimens.

Experimenters

The researcher for this study was the primary author, who has received extensive training in administering standardized tests through matriculation in a doctoral school psychology program**.** The researcher has previous experience calling NTPR participants and collecting data.

Setting

Interaction with the participants occurred solely through telephone interviews. All telephone calls were placed by the experimenter from the offices of the NTPR at Thomas Jefferson University. The examiner contacted the participants and administered DAYC questions verbally.

Materials

NTPR files, which contain the transplant recipients' contact information, medical history, and age of their children, were used in this study. Scoring sheets of the DAYC and the DAYC manual were needed for data collection and assessment.

Developmental Assessment Measure

The DAYC consists of a battery of five subtests that measure different but interrelated developmental abilities (Voress & Maddox, 1998). The subtests consist of the following developmental areas: cognition, communication, social-emotional development, physical development, and adaptive behavior. Each of the DAYC subtests is an area mandated by the IDEA. In this study, only two of the five subtests were administered; those subtests consisted of cognition and physical development. These

assessment areas were measured and a raw score in each area was obtained. The raw score was converted to a standard score.

Only two subtests were selected due to the amount of time needed to administer the tests over the phone. Each subtest takes approximately 10–20 minutes to administer. The test is designed to answer questions about the development of children from birth to age 5 years, 10 months (Voress & Maddox, 1998). Sample questions for the physical and cognitive scales are below. One point is scored for the items that a child can do right now, is beginning to do, or did when he/she was younger. DAYC data are recorded on subtest scoring forms.

Physical Development Subtest Sample Questions:

Age: Birth

- Extends both legs when lying on stomach
- Closes fingers when light pressure is applied on open palm

Age: 12 months

- Moves from back to sitting without assistance
- Picks up a small object using thumb and forefinger

Age: 24 months

- When standing, stoops, then stands again without losing balance
- Holds crayon, pencil, and so on, in fist with thumb up

Age: 36 months

- Walks backwards
- Uses one hand consistently in most activities

Age 48 months

- Hops on one foot a few steps
- Turns somersault

Cognitive Development Subtest Sample Questions:

Age: Birth

- Moves hand to mouth
- Watches an object moved slowly through his or her line of sight

Age: 12 months

- Transfers an object from one hand to the other to pick up a second object
- Hands an object to an adult to have that person repeat or start a desired action

Age: 24 months

- Demonstrates use of everyday items
- Places a small object into small container

Age: 36 months

- Stacks 6 to 7 blocks
- Matches simple shapes, such as circle, square, triangle

Age 48 months

- Imitates drawing of a face
- Sorts objects into categories; may not be able to label the categories

Additional recipient questions that were asked after the DAYC questions included the following:

- What is your current educational level?

- Is your child on any medications?
- Is your child healthy?
- Is your child developing well?
- Has your child had any surgeries?
- Is your child in school?
- Has your child participated in early intervention services* or special education?

  *Early intervention services consist of therapeutic and support services to infants and toddlers with developmental delays or disabilities. Services such as physical therapy, speech and language therapy, occupational therapy, and/or psychological services are provided to children in need.

Procedure

The examiner interviewed two groups of participants. One group consisted of female NTPR participants who have a child under the age of 6 that was exposed to tacrolimus in utero. The other group consisted of female NTPR participants who have a child under the age of 6 that was exposed to cyclosporine in utero. In this participant sample, no recipient was exposed to both medications during her pregnancy. Before the examiner began questioning the participant about her child's skills, she first established rapport with the parent. She began by introducing herself and identifying her association with the NTPR. She explained the purpose of the call, and briefly described the function and use of the DAYC. The examiner reassured the parent that her child is not expected to demonstrate all the skills asked during the interview and that many of the skills are seen in older children.

The examiner administered the DAYC via a telephone interview with the child's mother, went over each of the appropriate subtest items according to the child's age and scored the responses to the items as either "passed" (1 point) or "not passed" (0 points). The scores specify the performance of a child according to his/her mother's observation. The raw score, which is the total number of points that a person earns for the items of a subtest, was added. Raw scores were converted to age-based standard scores and percentiles to provide the clearest indication of a child's performance. The standard scores are based on a mean of 100 with a standard deviation of 15. Standard scores allowed the examiner to make meaningful comparisons across subtests. Percentiles represent values that indicate the percentage of the distribution that is equal to or below a particular score. The scores were not able to provide a diagnosis and score feedback was not provided to the mothers.

Research Design

The sample selection for this study consisted of those women who took either tacrolimus or cyclosporine during pregnancy, had a child under the age of 6 years old who was exposed in utero to the aforementioned medications, volunteered to be part of the NTPR, and agreed to answer questions about themselves and children. This non-equivalent control group design used groups that already existed: children exposed to cyclosporine in utero and children exposed to tacrolimus in utero. Thus, the independent variables in this study consisted of the two medications in this study, either the cyclosporine or the tacrolimus subjects. The dependent variables in this study consisted of the DAYC scores. Standard scores on the DAYC were calculated for the areas of physical and cognitive functioning for each subject. Additional maternal variables that

were analyzed include the mother's educational level, age of conception, kidney function during pregnancy based on creatinine level, and other maternal medications taken during pregnancy. Further variables about the children that were analyzed included whether the child had participated in early intervention services or special education, if the child had any previous surgeries, if the mother indicated her child was healthy, if the mother indicated her child is developing well, and if the child was currently on any medications.

Because there was a small sample size for this study, it was decided that it would not be reasonable to match the tacrolimus subjects to the cyclosporine subjects. In this study, the exact number of cyclosporine and tacrolimus participants were analyzed, despite the differences in the two sample sizes (cyclosporine $n = 23$, tacrolimus $n = 48$).

For a two-group design, the author expected a medium effect size, with an alpha of 0.05 and a statistical power of 80%, for the *t*-test comparing tacrolimus results to cyclosporine results. About 64 subjects would be needed to detect a medium effect size.

A one sample *t*-test, was used to compare group means (the tacrolimus or cyclosporine group) with the mean of the population (as determined by the DAYC normative sample). A MANOVA and two-sample t-test were used to compare the cyclosporine group to the tacrolimus group.

Furthermore, to compare the sample populations from the cyclosporine and tacrolimus groups, it was important to evaluate other variables about the transplant recipient, such as other medications they took during pregnancy, their age at conception, their educational level, and their kidney function during pregnancy based on their creatinine level. A MANCOVA analysis was used to compare these variables simultaneously. To compare child variables, such as whether the child had surgery, took

medication, was considered “healthy” and “developing well” by the mother, and had early intervention services, MANCOVA were also used. Lastly, to evaluate the cyclosporine and tacrolimus groups in terms of their differences across all variables together and separately, a two-group MANCOVA test was used.

CHAPTER 4

RESULTS

This research evaluated the areas of cognitive and physical development of children in the National Transplantation Pregnancy Registry (NTPR) database, under the age of 6, who were exposed to tacrolimus or cyclosporine in utero. Analysis of the research data involved exploring the possibility of statistically significant differences in cognition or physical abilities between those exposed children and the normative population used in the DAYC. Standard scores on the DAYC were obtained for each child in the study in the areas of cognition and physical development and were used for statistical analysis. This study addressed the following research questions:

1. Are statistically significant differences seen in cognitive development between the DAYC normative population and children exposed in utero to tacrolimus?
2. Are statistically significant differences seen in physical development between the DAYC normative population and children exposed in utero to tacrolimus?
3. Are statistically significant differences seen in cognitive development between children exposed in utero to cyclosporine verses children exposed in utero to tacrolimus?
4. Are statistically significant differences seen in physical development between children exposed in utero to cyclosporine verses children exposed in utero to tacrolimus?
5. Are statistically significant differences seen in cognitive development between the DAYC normative population and children exposed in utero to cyclosporine?

6. Are statistically significant differences seen in physical development between the DAYC normative population and children exposed in utero to cyclosporine?

Other areas that were also addressed in this study included child and maternal variables. Maternal variables that were evaluated included the mother's age at conception, the mother's educational level, mother's creatinine level during pregnancy, and the additional medications the mother took during her pregnancy. Child variables that were evaluated included current medications, surgical history, participation in early intervention or special education, and the parent's opinion on whether the child was "healthy" and/or "developing well."

The data were coded for ease of interpretation. The maternal and child variables were dummy coded into *yes* or *no* options. The coding on these variables were 0 = yes and 1 = no. For the medication options, the coding consisted of 0 = cyclosporine group and 1 = tacrolimus group. The Likert-type scale responses were used to code the maternal educational levels (0 = did not graduate high school, 1 = high school graduate, 2 = some college, 3 = college graduate, 4 = some postgraduate study, 5 = graduate degree). Responses that included *don't know* were viewed as missing data. Physical-standard scores on the DAYC were coded as PhySS. Cognitive-standard scores on the DAYC were coded as CogSS. In an attempt to explore all possible viewpoints posed by the research questions, multiple procedures including one sample *t*-tests, two-sample *t*-tests, regression analyses, MANOVAs, and MANCOVAs were conducted.

Demographics

The participants in this study were female kidney-transplant recipients located across the United States. Their average age of conception was 32 years old. Their average creatinine level during pregnancy, which indicates their kidney function, was 1.19. This level indicates an appropriate range for kidney function. Their current educational level fell in between "some college" and "college graduate" levels. Race, nationality, ethnicity, age, and income level were not asked of the recipients.

Further maternal demographic information can be analyzed when comparing the cyclosporine group to the tacrolimus group. The average age of conception for the cyclosporine group was 32.75 years old with a standard deviation of 3.51; the average creatinine level in the cyclosporine group was 0.99 with a standard deviation of 0.29. The average age of conception for the tacrolimus group was 31.26 with a standard deviation of 4.85. The average creatinine level for the tacrolimus group was 1.29 with a standard deviation of .46. In terms of educational level, Table 1 clarifies the educational levels of the study participants by medical group (cyclosporine or tacrolimus).

Table 1

Education Medical Group Crosstabulation

			Medical group		
			Cyclosporine	Tacrolimus	Total
Education	Did Not Graduate High School	Count	1 (33.3%)	2 (66.7%)	3
	High School Graduate	Count	2 (22.2%)	7 (77.8%)	9
	Some College	Count	5 (29.4%)	12 (70.6%)	17
	College Degree	Count	10 (40.0%)	15 (60.0%)	25
	Some Graduate School	Count	0	3 (100%)	3
	Graduate Degree	Count	5 (35.7%)	9 (64.3%)	14
Total		Count	23 (32.4%)	48 (67.6%)	71

The Table 2 lists the other medications that transplant recipients are prescribed concurrently with tacrolimus or cyclosporine. The following chart indicates the number of women who took these individual medications during pregnancy while also taking cyclosporine (n = 23) or tacrolimus (n = 48).

Table 2

Additional Medications Taken by Maternal Participants

Medication	Cyclosporine group	Tacrolimus group
Azathioprine	16	27
Antihypertensive	12	21
Mycophenolate mofetil	0	5
Sirolimus	1	1
Prednisone	21	41
Diabetic	2	8

In terms of child variables, there were 4 cyclosporine children and 7 tacrolimus children that reported to have surgery. There were also 4 cyclosporine children and 7 tacrolimus patients that reported to be on medication. Three children from the

cyclosporine group and five children from the tacrolimus group participated in early intervention services.

Research Question 1

Are there statistically significant differences between the DAYC scores in cognitive development of children exposed in utero to tacrolimus and the DAYC normative population?

To answer Research Question 1, a one-sample *t*-test with cognitive standard scores as the dependent variables and the tacrolimus group as the independent variable was used. In this analysis, the DAYC normative mean of 100.0 was compared to the tacrolimus group mean of 105.1. The standard deviation was 12.5 and the sample size for this analysis was $n = 47$. This one-sample *t*-test resulted in a significant difference between the normative mean and the tacrolimus group mean, where $t = 2.81$ and $p < .01$. The effect size for this significant result is .41, which is between a small and medium effect size for Cohen's *d*. Thus, children exposed to tacrolimus in utero showed statistically significant higher cognitive mean scores (105.1) than the DAYC normative sample mean score (100.0).

Finding for Research Question 1

Exposure to tacrolimus in utero did not show a negative effect in children's cognitive ability. Rather, children exposed to tacrolimus had significantly higher cognitive levels compared to the normative sample.

Research Question 2

Are there statistically significant differences between the DAYC scores in physical development of children exposed in utero to tacrolimus and the DAYC normative data?

To answer Research Question 2, a one sample *t*-test, with physical-development standard scores as the dependent variables and the tacrolimus group as the independent variable, was used. In this analysis, the DAYC normative mean of 100.0 was compared to the tacrolimus group mean of 100.23. The standard deviation was 10.62 and the sample size for this analysis was $n = 47$. This one-sample *t*-test did not result in a significant difference between the normative mean and the tacrolimus group mean, where $t = .15$ and $p = .88$ (two-tailed). Thus, children exposed to tacrolimus in utero did not show significantly significant differences between their physical development mean standard score of 100.23 and the DAYC normative mean value of 100.00.

Finding for Research Question 2

Exposure to tacrolimus in utero did not show a negative effect in children's physical skills.

Research Question 3

While research questions 3 and 4 were analyzed together, their results are displayed and analyzed separately to better clarify their individual answers. Research question 3 focuses on cognitive scores. Are there statistically significant differences of the DAYC cognitive scores and DAYC physical scores between the children exposed in utero to cyclosporine versus the children exposed to Tacrolimus?

A MANOVA was first conducted with the independent variable of medication group (tacrolimus or cyclosporine) and the dependent variables of CogSS and PhySS. The medication group was not found to be significant. The Box's test was performed and passed the equality of covariance matrices, which tests the null hypothesis that the observed covariance matrices of the dependent variables are equal across groups. The Wilks' Lambda effect for the medication group was equal to .954 and not significant, with F (2.0, 67) = 1.60 and p = .21. The Levene's test of equality of error variances was not significant at $p > .01$. When not controlling for other variables, there were no differences between the cyclosporine and tacrolimus groups.

The second approach to answering Research Question 3 used a two-sample *t*-test, using the unadjusted means for both the cyclosporine group (Medication Group 0) and the tacrolimus group (Medication Group 1) for cognitive skills. This analysis revealed no statistically significant difference between the cyclosporine group mean of 107.83 and the tacrolimus group mean of 104.54 for cognitive development. It should be noted, however, that this analysis used the unadjusted mean, which did not control for any variables. The Levene's test was passed for the *t*-test, indicating that equal variances were assumed. The mean difference was found to be nonsignificant at 3.28 points with a *t*-value of 1.09. Thus, there were no significant differences found between the cyclosporine group and the tacrolimus group (p = .279; see Table 3).

Table 3

Group Statistics for the t-Test

Dependent variable	Medical group	*N*	Mean	Standard deviation	Standard error mean
Cognitive-standard score	Cyclosporine	23	107.83	9.18	1.91
	Tacrolimus	48	104.54	12.95	1.87

Next, a MANCOVA was used to control for the child variables. Child variables included whether the mother indicated that the child had surgery, is currently on medication, received early-intervention services, and was "healthy" and/or "developing well." These covariates were included in the MANCOVA because they made theoretical sense as possibly impacting the outcome variable. There was no statistical significance found between the adjusted mean of the cyclosporine group (108.28) and the adjusted mean of the tacrolimus group (104.88) in cognitive scores; the difference between the cyclosporine and tacrolimus means was 3.40 with a standard error of 2.8 with $p > .01$. (see Table 4).

Table 4

Results of the MANCOVA on Child Health Variables Using the Cognitive-Standard Score as the Dependent Variable

				95% Confidence interval	
Dependent variable	Medical group	Mean	Standard error	Lower bound	Upper bound
Cognitive-standard score	Cyclosporine	108.28[a]	2.28	103.72	112.85
	Tacrolimus	104.88[a]	1.59	101.70	108.06

Covariates appearing in the model are evaluated at the following values: Health = .01, Develop = .00, Surgery = .86, Meds = .86, EIService = .90.

The Box's test was performed and passed the equality of covariance matricies. The Levene's test of equality of error variances was not significant at $p > .01$. The

Wilks' Lambda effect for the different child variables was not significant except for one variable: early-intervention services. The Wilks' Lambda for early-intervention services had a value of .874, F (2.0, 63) = 4.54 and a p = .014. Table 5 shows the significance of the early-intervention-service variable when evaluated for CogSS. Early intervention services are interventions provided to help infants and toddlers who have a developmental delay or disability in the areas of physical, cognitive, communication, social/emotional, or self-help abilities. Those children who received early-intervention services, such as speech therapy, occupational therapy, or physical therapy, scored on average 13.98 points less on their CogSS. Thus, there was a significant correlation between early-intervention services and lower scores on the cognitive-development assessment for children exposed to either cyclosporine or tacrolimus.

Table 5

Tests of Between-Subject Effects for Child Variables

Variable	Dependent variable	*F*	Sig.	Partial eta squared
Corrected Model	Cognitive-standard scores	2.60	0.033	.169
Intercept	Cognitive-standard scores	308.49	0	.828
Health	Cognitive-standard scores	0.30	0.58	.005
Developing well	Cognitive-standard scores	.	.	
Previous Surgery	Cognitive-standard scores	0.75	0.39	.012
Current Medications	Cognitive-standard scores	0.12	0.73	.002
Early Intervention	Cognitive-standard scores	8.29	0.005	.115
Medical Group (C/T)	Cognitive-standard scores	1.48	0.23	.023

To further analyze the mother's variables, such as her age of conception, creatinine level during pregnancy, educational level, and the additional medications she was taking concurrently with either tacrolimus or cyclosporine, another MANCOVA was

used. For the MANCOVA tables below, the Medical Group (cyclosporine or tacrolimus) had a Wilks' lambda value of .922, F (2.0, 51) = 2.154 and a significance level of .126. The Levene's test of equality was non-significant for cognitive scores. Tables 6 and 7 show that the mother's variables did not show a significant effect on the dependent variable of cognitive scores. The pairwise comparison table also shows cognitive development scores as non-significant. Thus, for cognitive development, when controlling for maternal variables, the mean difference between the cyclosporine mean (108.32) and the tacrolimus mean (105.13) was 3.19 with a standard error of 3.80 and a significance value of >.1.

Table 6

Tests of Between-Subjects Effects for Mother Variables

Source	Dependent variable	*F*	Sig.	Partial eta squared
Corrected Model	Cognitive-standard scores	.525	.865	.092
Age of Conception	Cognitive-standard scores	.037	.848	.001
Creatinine Pregnancy	Cognitive-standard scores	.861	.358	.016
Educational level	Cognitive-standard scores	.170	.681	.003
Med-Azathioprine	Cognitive-standard scores	.673	.416	.013
Med-Antihypertensive	Cognitive-standard scores	.291	.592	.006
Med-MM	Cognitive-standard scores	.261	.611	.005
Med-Sirolimus	Cognitive-standard scores	.640	.428	.012
Med-Prednisone	Cognitive-standard scores	.081	.776	.002
Med-Diabetes med	Cognitive-standard scores	1.492	.227	.028
Medical Group (C/T)	Cognitive-standard scores	.706	.405	.013

Table 7

Estimates and Pairwise Comparisons

Dependent variable	Medical group	Mean	Standard error	95% Confidence interval	
				Lower bound	Upper bound
Cognitive-standard scores	Cyclosporine	108.28[a]	3.02	102.26	114.34
	Tacrolimus	105.13[a]	1.97	101.18	109.07

a. Covariates appearing in the model are evaluated at the following values: AgeConcep = 31.73, CreatPreg = 1.193, Education = 2.84, MedAza = .43, MedAnti = .56, MedMM = .94, MedSir = .97, MedPre = .13, MedDBs = .86.

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Finding for Research Question 3

When not controlling for variables, no differences were seen in cognitive ability between the cyclosporine or tacrolimus groups. However, when controlling for child and mother variables, children receiving early-intervention services had lower cognitive ability.

Research Question 4

Are there statistically significant differences on the DAYC physical scores between the children exposed in utero to cyclosporine versus the children exposed to Tacrolimus?

The MANOVA used to answer Research Question 3 was also used to answer Research Question 4. The MANOVA was conducted with the independent variable of medication group (tacrolimus or cyclosporine) and the dependent variables of the CogSS and PhySS. The medication group was not found to be significant. When not controlling for other variables, there were no significant differences between the cyclosporine and tacrolimus groups at the $p < .05$ level. However, there was significance seen at the

$p < .10$ level with a 4.68 point mean difference between the cyclosporine group and the tacrolimus group (see Table 8).

Table 8

Tests of Between-Subjects Effects for Physical Standard Scores

Source	Dependent variable		*F*	Sig.
Corrected Model	Dimension 1	Physical-standard score	3.226	.077
Intercept	Dimension 1	Physical-standard score	6201.634	.000
Medical Group (C/T)	Dimension 1	Physical-standard score	3.226	.077

The second approach to answering Research Question 4 used a two-sample *t*-test shown below [see Table 9]. It should be noted, however, that this analysis used the unadjusted mean, which did not control for any variables. This analysis showed that there was no significant difference between the cyclosporine physical-development mean score of 104.91 and the tacrolimus physical-development mean score of 100.23 on the DAYC.

Table 9

Group Statistics for t-Test

Dependent variable	Medical group	*N*	Mean	Standard deviation	Standard error mean
Physical-standard score	Cyclosporine	23	104.91	9.376	1.955
	Tacrolimus	47	100.23	10.624	1.550

When reviewing the Levene's test for equality of variances, the PhySS passed and the equal variances assumed were significant at the $p > 0.1$ value (see Tables 10 and 11).

Table 10

Results of Independent Samples Test

		t-test for equality of means		
		Sig. (2-tailed)	Mean difference	Standard error difference
Physical-standard score	Equal variances assumed	.077	4.679	2.605
	Equal variances not assumed	.067	4.679	2.495

Although the MANOVA and *t*-test above did not show significance at the $p < .05$ level between the tacrolimus and cyclosporine groups for physical-development scores, further analyses that control for child and maternal variables were analyzed because of their possible impact on the outcome variables. The MANCOVA results shown in Tables 11, 12, and 13 controlled for child health variables. They indicated that a child's participation in early-intervention services was significant at $p = .053$. The medical group of either cyclosporine or tacrolimus is also significant at the $p < .05$ level. When controlling for children's health variables, the tacrolimus group showed a lower score in physical development by 5.42 points compared to the cyclosporine group (standard error = 2.54). Those children exposed to tacrolimus received lower scores for their physical development compared to children in the cyclosporine group.

Table 11

Tests of Between-Subjects Effects for Child Variables

Source	Dependent variable		*F*	Sig.	Partial eta squared
Healthy	Dimension 1	Physical-standard scores	.105	.746	.002
Developing Well	Dimension 1	Physical-standard scores	Not calculated due to lack of variation		
Previous Surgery	Dimension 1	Physical-standard scores	.122	.728	.002
Current Medications	Dimension 1	Physical-standard scores	1.737	.192	.026
Early Intervention	Dimension 1	Physical-standard scores	3.871	.053	.057
Medical Group (C/T)	Dimension 1	Physical-standard scores	4.545	.037	.066

Table 12

MANCOVA Estimates

					95% confidence interval	
Dependent variable	MedGroup		Mean	Standard error	Lower bound	Upper bound
Physical-standard score	Dimension 1	0	105.409[a]	2.076	101.261	109.557
		1	99.991[a]	1.448	97.099	102.884

a. Covariates appearing in the model are evaluated at the following values: Health = .01, Develop = .00, Surgery = .86, Meds = .86, EIService = .90.

Table 13

Univariate Tests

Dependent variable		Sum of squares	*df*	Mean square	*F*	Sig.
Physical-standard score	Contrast	445.120	1	445.120	4.545	.037
	Error	6267.796	64	97.934		

The *F* tests the effect of MedGroup. This test is based on the linearly independent pairwise comparisons among the estimated marginal means.

To control for maternal variables, the MANCOVA results shown in Tables 14 and 15 evaluated the mother's age of conception, creatinine during pregnancy, education level, other medications taken concurrently with cyclosporine or tacrolimus, and the medical group (cyclosporine or tacrolimus). Wilks' lambda values for all variables were

not significant except for the mother's educational level variable. The mother's educational level had a Wilk's lambda of .840 with an *F* score of 4.85, a significance level of .012, and a partial eta squared of .160. The Levene's test of equality was nonsignificant for physical scores. When controlling for the maternal variables, the difference between the cyclosporine group mean (106.15) and the tacrolimus group means (99.6) were significant for physical abilities. The mean difference between the two groups was 6.54 points with a standard error of 3.15 and significance level $p < .05$.

Table 14

Tests of Between-Subjects Effects for Mother Variables

Source	Dependent variable	*F*	Sig.	Partial eta squared
Corrected Model	Physical-standard scores	1.406	.204	.213
Intercept	Physical-standard scores	76.265	.000	.595
Age of Conception	Physical-standard scores	.015	.902	.000
Creatine Pregnancy	Physical-standard scores	.383	.539	.007
Educational level	Physical-standard scores	5.879	.019	.102
Med-Aza	Physical-standard scores	.352	.555	.007
Med-Antihypertensiv	Physical-standard scores	.571	.453	.011
Med-MM	Physical-standard scores	.154	.697	.003
Med-Sirolimus	Physical-standard scores	.642	.427	.012
Med-Prednisone	Physical-standard scores	.617	.436	.012
Med-Diabetic	Physical-standard scores	1.474	.230	.028
Medical Group (C/T)	Physical-standard scores	4.299	.043	.076

Table 15

MANCOVA Estimates When Controlling for Mother Variables

Dependent variable	MedGroup	Mean	Standard error	95% Confidence interval	
				Lower bound	Upper bound
Physical-standard score	0	106.146[a]	2.508	101.113	111.180
	1	99.606[a]	1.631	96.334	102.879

a. Covariates appearing in the model are evaluated at the following values: AgeConcep = 31.73, CreatPreg = 1.193, Education = 2.84, MedAza = .43, MedAnti = .56, MedMM = .94, MedSir = .97, MedPre = .13, MedDBs = .86.

When related to physical development, the aforementioned independent variables were found to be nonsignificant. However, after controlling for those variables, it was found that the medication group to which the child was exposed in utero (either cyclosporine or tacrolimus) was significant ($p < 0.05$). Those children exposed to tacrolimus received lower scores for their physical development compared to children in the cyclosporine group.

Furthermore, the child's early-intervention status, the child's exposure to medication (either cyclosporine or tacrolimus), and the child's mother's educational level all correlated with the child's physical ability. For early-intervention services, the children with these services scored 10.42 points lower on the physical-development assessment than children without the services. In the tacrolimus versus cyclosporine groups, those children exposed to tacrolimus scored 8.07 points lower on physical ability than those in the cyclosporine group. Lastly, higher educational level of the mother correlated with lower physical standard scores by 2.16 points.

To summarize, this analysis showed no significant difference ($p < .05$) between the unadjusted cyclosporine physical-development mean score (104.91) and the

unadjusted tacrolimus physical-development mean score (100.23) on the DAYC. However, when controlled for children's health variables, the adjusted mean showed significance; children exposed to tacrolimus in utero showed a lower (adjusted) physical-development standard score by 5.4 points compared to children exposed to cyclosporine in utero. When controlling for maternal variables, there was also significance: children exposed to tacrolimus in utero showed a significantly lower (adjusted) physical-development standard score by 6.5–8.0 points compared to children exposed to cyclosporine in utero. Furthermore, the mother's educational level showed significance: as the mother's educational level increased, the PhySS decreased by 2.6 points. Lastly, a child's participation in early-intervention services showed significance: children who participated in early intervention received a decreased PhySS by 10 points.

Finding for Research Question 4

When not controlling for variables, neither children exposed to cyclosporine or tacrolimus in utero had negative effects from the medications in their physical development. However, when controlling for children's health or maternal variables, children exposed to tacrolimus showed lower physical ability compared to cyclosporine exposed children. Furthermore, the mother's educational level impacted her child's physical development: mothers with higher educational levels had children with slightly lower physical-development skills. Also, children who participated in early intervention had lower physical ability.

Research Question 5

Are there statistically significant differences between the DAYC scores in cognitive development of children exposed in utero to cyclosporine and the DAYC normative data?

To answer Research Question 5, a one-sample *t*-test with cognitive scores as the dependent variables and the cyclosporine group as the independent variable, was used. In this analysis, the DAYC normative mean of 100.0 was compared to the cyclosporine group mean of 107.8. The standard deviation was 9.2 and the sample size for this analysis was $n = 23$. This one-sample *t*-test resulted in a significant difference between the normative mean and the cyclosporine group mean, where $t = 4.09$ and $p < .01$. The effect size for this significant result is .85, which is a large effect size for Cohen's *d*. Thus, children exposed to cyclosporine in utero showed statistically significant higher cognitive mean scores (107.8) than the DAYC normative sample mean score (100.0).

Finding for Research Question 5

Children exposed to cyclosporine in utero scored higher in cognition than the normative population. This indicates that children in this study did not have a detrimental effect in cognitive development from being exposed to cyclosporine in utero.

Research Question 6

Are there statistically significant differences between the DAYC scores in physical development of children exposed in utero to cyclosporine and the DAYC normative data?

To answer Research Question 6, a one-sample *t*-test with physical scores as the dependent variables and the cyclosporine group as the independent variable, was used. In

this analysis, the DAYC normative mean of 100.0 was compared to the cyclosporine group mean of 104.9. The standard deviation was 9.4 and the sample size for this analysis was $n = 23$. This one-sample *t*-test resulted in a significant difference between the normative mean and the cyclosporine group mean, where $t = 2.51$ and $p = .019$. This was significant at the $p < .05$ value. The effect size for this significant result is .52, which is a medium effect size for Cohen's *d*. Thus, children exposed to cyclosporine in utero showed statistically significant higher physical-development mean scores (104.91) than the DAYC normative group (mean = 100.0).

Findings for Research Question 6

Children exposed to cyclosporine in utero scored higher for their physical abilities than the normative population. This indicates that children in this study did not have a negative effect from exposure to cyclosporine in utero for physical development skills.

In Chapter 4, an analysis of the raw data was obtained and a presentation of the findings was shown. Each of the six research questions was addressed. A summary of the research questions and findings can be seen in Table 16. Chapter 5 discusses the findings and presents a conclusion.

Table 16

Summary of Research Questions and Findings

Research questions	Research findings
1)Are there statistically significant differences between the DAYC scores in cognitive development of children exposed in utero to tacrolimus and the DAYC normative?	Children exposed to tacrolimus had higher cognitive levels compared to the normative sample.
2)Are there statistically significant differences between the DAYC scores in physical development of children exposed in utero to tacrolimus and the DAYC normative data?	Exposure to tacrolimus in utero did not show a negative effect in children's physical skills.
3)Are there statistically significant differences of the DAYC cognitive scores between the children exposed in utero to cyclosporine versus the children exposed to tacrolimus?	When not controlling for variables, no differences were seen in cognitive ability between the tacrolimus or cyclosporine groups. However, when controlling for child and mother variables, children receiving early intervention services had lower cognitive ability.
4)Are there statistically significant differences of the DAYC physical scores between the children exposed in utero to cyclosporine versus the children exposed to tacrolimus?	When not controlling for variables, children exposed to cyclosporine or tacrolimus in utero had no negative effects from the medications in terms of their physical development. However, when controlling for maternal or children's health variables, children exposed to tacrolimus showed lower physical ability as compared to cyclosporine children. Furthermore, the mother's educational level impacted her child's physical development; mothers with higher educational levels had children with slightly lower physical development skills. Also, children who participated in early intervention had lower physical ability.
5)Are there statistically significant differences between the DAYC scores in cognitive development of children exposed in utero to cyclosporine and the DAYC normative data?	Children exposed to cyclosporine in utero scored higher in cognition than the normative population. This indicates that children in this study did not have a detrimental effect in cognitive development from being exposed to cyclosporine in utero.
6) Are there statistically significant differences between the DAYC scores in physical development of children exposed in utero to cyclosporine and the DAYC normative data?	Children exposed to cyclosporine in utero scored higher for their physical abilities than the normative population. This indicates that children in this study did not have a negative effect from exposure to cyclosporine in utero for physical development skills.

CHAPTER 5

DISCUSSION

Summary of the Purpose and Results

The purpose of this study was to investigate the developmental effects of tacrolimus or cyclosporine medication on the offspring of female kidney-transplant recipients who have been treated with those immunosuppressive drugs during pregnancy. Specifically, the cognitive and physical development of children between the ages of 4 months to 5 years, 10 months old was explored using the DAYC. Assessments of children exposed in utero to tacrolimus were studied and compared to the assessments of those exposed in utero to cyclosporine and both sets of children were compared to the normative population.

Secondary research questions were also explored. The mother's age of conception, creatinine level during pregnancy, educational level, and concomitant medications she was on during pregnancy were analyzed and compared to the developmental data. Aspects about the recipient's children, such as whether they have had surgery, currently take medication, participated in early intervention or special education, and are considered "healthy" and "developing well" by their mother were also considered and reviewed.

The results of this research indicate findings to the six research questions addressed in the previous chapters. Findings from Research Question 1 showed that children exposed to tacrolimus had higher cognitive levels compared to the normative sample.

It can be concluded that exposure to tacrolimus did not have a negative effect on children's cognition. Rather, compared to a normative population sample, children exposed to tacrolimus may have benefitted from exposure to this medication in utero. The reason why these children may have benefitted from exposure to this medication would be difficult to ascertain; the children may have benefitted from the medication itself or from other unknown variables. Further exploration of possible reasons as to why children may have benefitted are explored later in this chapter. However, this study shows that pregnant women who take tacrolimus will not harm their child's cognitive development. This research concurs with the previous findings of Garcia-Donaire et al. (2005), who suggested that pregnancy with tacrolimus medication is safe and effective, with close monitoring. Garcia-Donaire et al. (2005) found favorable pregnancy outcomes without any major effects on intrauterine growth and no observable pharmacological side effects.

Findings from Research Question 2 showed that children exposed to tacrolimus in utero did not show any negative effects in their physical ability. It can be implied that having exposure to tacrolimus in utero does not have a negative impact on the physical development of children.

The conclusion that can be drawn from this finding is that women given tacrolimus during pregnancy do not need to be concerned that it will harm the physical ability of their children. The research of Garcia-Donaire et al. (2005) also found similar results, finding no major effects on intrauterine growth, no anomalies, no major incidence of malformations, no need for breathing support, and no observable pharmacological side effects of children exposed to tacrolimus in utero.

No current literature was found showing the relationship between tacrolimus and any developmental or cognitive problems in the offspring. Overall, the research is limited on the effects tacrolimus may have on exposed offspring of transplant recipients. The conclusions from Research Questions 1 and 2 in this study help provide evidence that exposure to tacrolimus has not indicated problems with cognitive or physical development in young children. From this study, practitioners prescribing tacrolimus can be reassured that the drug does not show harmful effects in cognitive or physical development to the children exposed to it.

Findings from Research Question 3 show no differences in cognitive ability between the tacrolimus and cyclosporine groups when not controlling for variables. However, when controlling for child and mother variables, children receiving early-intervention services had lower cognitive ability.

It can be concluded from Research Question 3 findings that children exposed to tacrolimus or cyclosporine in utero who require the assistance of early-intervention services have lower cognitive abilities. Children who participate in early-intervention services have displayed a previous developmental delay or disability to warrant the intervention. Early-intervention strategies have been developed to improve cognitive skills and enhance potential long-term outcomes (Holt & Mikati, 2011; Nordhov et al., 2010). These children may continue to perform at lower cognitive levels compared to those children who did not require these services. In this study, children who required early-intervention services showed lower CogSS. Thus, while neither medication showed a negative effect on children's cognition, children in need of extra assistance through early-intervention services had lower cognitive skills. This is beneficial information for a

child's pediatrician or school psychologist to be aware of when evaluating a child who has participated in early-intervention services.

Findings from Research Question 4 indicated no differences in physical ability between those children exposed to cyclosporine versus those children exposed to tacrolimus in utero. However, when child and mother variables were taken into consideration, there were significant concerns. When controlling for children's health variables or maternal variables, children exposed to tacrolimus in utero showed decreased physical ability compared to children exposed to cyclosporine. It may be concluded that cyclosporine medication may have a higher positive impact on children's physical ability as compared to tacrolimus' effects. The reason for this higher impact is difficult to ascertain, and other variables may play a role in causing the higher physical scores.

Furthermore, the mother's educational level had an impact on her child's physical ability. The more education the mother had, the lower her child's physical-development level. This is beneficial information for a physician or mother to know; children of mothers with higher levels of education exposed to these medications do not show higher levels of physical development. This could be due to a variety of reasons. A study by Marcon (1999) found that gross motor skills of preschool children were lower in preschool programs that had a strong academic focus. Perhaps mothers with higher educational levels tend to focus on cognitive skills more than physical skills with their children. Another reason could perhaps be that these mothers return to work earlier than mothers with lower levels of education and thus do not spend as much time with their children doing physical activities. While other environmental or social factors can have

an influence on the physical development of children and should be considered, those variables were beyond the scope of this research.

Lastly, children who participated in early-intervention services showed lower physical ability. This is not surprising because those children who need early-intervention services may need the help of a physical or occupational therapist for their physical needs. Medical providers can benefit from this information when evaluating a child who participated in early-intervention services.

Findings from Research Question 5 showed that children exposed to cyclosporine in utero scored higher in cognition than the normative population. This indicates that children in this study did not have a detrimental effect in cognitive development from being exposed to cyclosporine in utero.

Nulman et al. (2010) found no association between in utero exposure to cyclosporine and children's' long-term neurocognitive development, compared to unexposed healthy children. Sifontis et al. (2006) did not find neurocognitive issues in children exposed to cyclosporine in utero. This study concurred with the aforementioned studies. It can also be concluded from this study that cyclosporine has a beneficial effect on children's cognition compared to the normative population. The reason why children in this study showed higher cognitive scores and thus benefitted from the cyclosporine exposure is difficult to ascertain and may be due to other variables outside the scope of this research. Nonetheless, healthcare providers and school psychologists would benefit from the knowledge that cognition may be higher in children exposed to cyclosporine in utero.

Findings from Research Question 6 indicated that children did not have a negative effect from exposure to cyclosporine in utero for physical-development skills. In fact, children exposed to cyclosporine in utero scored higher in physical ability than the normative population. This finding concurs with Armenti et al. (2006), who did not find increased evidence of congenital malformations in humans exposed to cyclosporine, and with Josephson and McKay (2010), who found no increased risk of birth defects for those children exposed to cyclosporine.

It can be concluded that because PhySS were higher for those children exposed to cyclosporine in utero in this study, exposure to that medication may show positive outcomes on children's physical ability. However, based on this limited study, more studies evaluating other variables would be needed to come to a definitive conclusion about cyclosporine's beneficial effect on physical and cognitive development.

It should be further noted that higher scores for cognitive development seen from children exposed to either cyclosporine or tacrolimus (compared to the normative DAYC population) may be due to a variety of reasons. First, being exposed to cyclosporine or tacrolimus in utero may indeed cause a change in neonatal neurological development causing higher cognitive skills in children. A second reason may be that mothers who have received a kidney transplant and take cyclosporine or tacrolimus may report higher abilities or skills of their children than the normative sample. Mothers in the NTPR may be more observant or vigilant about their children's abilities due to their own concerns about any medication effects. Apprehension regarding possible medication effects on their child's health is an expressed concern from transplant recipients (Coscia et al., 2009), and these parents may be more observant of their children's abilities and skills

than the general population. Another reason may be due to other environmental or social variables that cause a change in utero to these children. For example, women who receive a kidney transplant may eat healthier or visit a physician for their physical health more often than women without health concerns. Certainly, this specific population of women in the NTPR may be different from the general sample population used for DAYC normative scoring. A fourth reason may be due to the Flynn effect, which is an increase in standard scores on intelligence tests over time. Since the DAYC was first published in 1998, the 13-year difference between its publication and the data collected in this study may indeed be a big enough time difference to show an increase in the scores. Of course, these aforementioned reasons are speculative in nature, as this research did not find causation, only correlation.

Research Limitations

The results of this research can help provide school psychologists, physicians, nurses, and parents with a greater understanding of possible immunosuppressive medication effects on children who were exposed to cyclosporine and/or tacrolimus in utero. The research design of this study yielded many advantages. First, the design decreased participant reactivity and experimental bias. Because the researcher's contact with the participants was conducted completely over the phone, the use of body language, eye contact, and behavioral concerns on the part of the researcher did not come into play. The experimenter asked the standardized questions exactly as indicated on the DAYC forms, requesting a *yes/no* response. This form of research reduces experimenter bias as well as promotes measures of standardization. Another advantage of this research design was that all eligible participants in this study were contacted. Thus, the selection of

subjects was not biased. However, there were limitations to this research, including bias responses, sampling bias, small sample size, and unbalanced design.

Although participants were assured that their responses to the questions were confidential and scores or feedback would not be provided, it is possible that participants engaged in biased responding in an effort to promote social desirability; mothers were asked to report on a sensitive topic—their child's abilities, physical level, and academic skills—and social desirability may have led them to report inflated levels for their children. Therefore, a discrepancy may exist between the children's actual abilities or skills and reported levels (Agnew & Pike, 1994; Holden & Passey, 2009). Consequently, the reliance on the mothers' self-report of their children in this study is a limitation that could have affected the study's internal validity. Direct observation of the children by a future experimenter may provide a more accurate picture of the children's' actual abilities and skills. However, for this study, the distance between the experimenter and the children, who were located across the United States, made this option too difficult.

Sampling bias may exist because the kidney-transplant recipients involved in this study were all women who agreed to be a part of the NTPR, volunteered to partake in this study, made themselves reachable and assessable by phone, and spent the time to answer the multitude of questions without receiving any reward. Thus, this study did not include transplant recipients who were unreachable by phone, who were reachable but were too busy at the time of the study to answer questions, who did not speak English, or who were not part of the NTPR database. Sampling bias could have an effect on the external validity of the study, because the women involved in the study may not be generalized to

the rest of the female kidney-transplant population. Involving recipients from other transplant databases, lengthening the time of the study to reach more recipients, and/or using an interpreter for non-English-speaking patients could have helped with any sampling bias limitations.

An additional limitation to this study was that it did not have a balanced design. Tacrolimus is currently prescribed much more frequently than cyclosporine. Thus, this study had only 23 children exposed to cyclosporine and 49 children exposed to tacrolimus. Because the study already had a small total sample size of 72 children, it was decided that matching the tacrolimus sample to the cyclosporine sample would greatly limit the number of subjects in the study, which would affect the external validity of the study. Furthermore, the dosage of the mother's medication was not considered in this research. Different dosages of the mother's medications may have had different influences on the child in utero.

Lastly, other factors that could have affected the validity of the DAYC scores include the degree of rapport participants felt with the experimenter, the participants' understanding of the instructions and the specific questions, and participants' English-language skills. Although the children's' wide age ranges (from 4 months old to 5 years and 10 months old) may appear to be a limitation, administration of the DAYC, an age-standardized test, corrected for the age difference.

Implications for the Field

Although research continues to examine the effects of immunosuppressant drugs in the children of transplant recipients, currently there is limited information regarding the toxicities and teratogenic potentials of these medications, especially when exploring

any long-term implications. The current finding that children who have been exposed to cyclosporine or tacrolimus in utero show higher cognitive-development levels than the normative data can provide reassurance to transplant recipients who are thinking of becoming pregnant or have children, as well as reassurance to physicians when treating transplant recipients with cyclosporine or tacrolimus. Furthermore, the current finding that children exposed in utero to cyclosporine show higher levels of physical development compared to normative data and children exposed to tacrolimus in utero show similar physical-development levels to the normative data also can provide reassurance. School psychologists can benefit from this information when evaluating a child with a history of exposure to these medications in utero. These encouraging results concerning cyclosporine and tacrolimus exposure in utero may help aid school psychologists and medical-care providers when making evidence-based decisions.

As more female kidney transplant recipients maintained on immunosuppressive therapy have opted to become pregnant, knowledge has increased about the effects of these medications on the child. This study has contributed and concurred with previous studies, such as Armenti et al. (2006), Garcia-Donaire et al. (2005), Josephson and McKay (2010), Nulman et al. (2010), and Sifontis et al. (2006), that cyclosporine and tacrolimus do not show direct detrimental effects on the exposed child's development.

Suggestions for Future Research

The current research helped provide a better understanding of the cognitive and physical developmental of children under the age of 6 years old who were exposed to tacrolimus or cyclosporine in utero. Future research may wish to consider replicating this study by conducting the research over a longer period of time. As mothers continue to

have more children over the years while taking immunosuppressant medications, a larger sample size can be obtained. Another possible way to increase sample size would be to include mothers from other transplant registries, such as the European Dialysis and Transplant Association Registry and the United Kingdom Transplant Registry. Future research may also benefit from using a longitudinal research design, in order to highlight the existence of any long-term consequences from exposure in utero to immunosuppressive medications. Other standardized measures may also be used to help confirm this data and increase the validity of the results. This study only involved children under the age of 6 years old, due to the age restrictions of the DAYC; future research would benefit from evaluating older children exposed to these medications using different assessment measures. Furthermore, it would be beneficial to study the offspring of the children in this study to determine if any possible effects of the medication in utero perhaps had an effect on their offspring's development.

Conclusion

This study specifically evaluated the physical and cognitive areas of development in children under the age of 6 years old who were exposed to tacrolimus or cyclosporine in utero. Overall, findings suggest that compared to an unexposed normative sample population from the DAYC, children exposed to cyclosporine or tacrolimus in utero do not show negative cognitive or physical effects from those medications and in fact, children showed higher levels of cognition. Other factors should be considered in future research to come to a definitive conclusion about the potential benefits of these medications. Those children who received early-intervention services, however, reported lower cognitive and physical scores compared to the normative population. While the

safety of cyclosporine and tacrolimus medications in pregnancy have not been endorsed by their manufacturers (Grimer, 2007), these results help provide provisional reassurance to transplant recipients and medical-care providers about the exposed offspring. This information may also aid school psychologists when evaluating children with exposure to these medications.

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APPENDIX: RAW DATA

ID	Gender	AgeMo	PhyRS	PhySS	PhyPer	CogRS	CogSS	CogPer	Health	Develop	Surgery	Meds	EIService	AgeConcep	CreatPreg	Education	MedGroup	MedAza	MedAnti	MedMM	MedSir	MedPre	MedDBs
134d	0	7	14	82	12	6	89	23	0	0	1	1	1	40	1.8	2	1	1	0	1	1	0	1
134c	1	31	65	107	68	39	101	53	0	0	0	1	1	38	1.3	2	1	1	0	1	1	0	1
125a	1	70	86	105	63	68	94	34	0	0	1	1	1	29	0.8	2	0	1	0	1	1	0	1
125b	0	44	69	95	37	56	107	68	0	0	1	1	1	31		2	0	1	0	1	1	0	1
125c	1	12	50	111	77	20	104	61	0	0	1	1	1	33	0.7	2	0	1	1	1	1	0	1
58c	1	12	42	91	27	23	115	84	0	0	1	1	1	33	1.4	3	1	0	0	1	1	0	0
124a	1	20	53	99	47	24	91	27	0	0	1	0	1	26	1.9	3	1	1	0	1	1	0	1
87a	0	50	73	93	32	59	96	39	0	0	1	1	1	37	1.1	5	1	0	1	1	1	0	1
129a	1	37	82	127	96	60	126	96	0	0	1	1	1	31	0.9	3	0	0	0	1	1	0	1
120a	0	21	55	105	63	31	112	79	0	0	0	1	1	26	1.1	3	1	0	1	1	1	0	1
74c	1	59	84	108	70	77	126	96	0	0	1	1	1	36	1.0	3	1	0	1	1	1	0	1
91a	0	44	70	96	39	60	115	84	0	0	1	1	1	33	1.2	2	1	0	1	1	1	0	1
13bII	0	4	21	103	58	9	107	68	0	0	1	0	1	37	0.6	3	0	1	1	1	1	1	1
133b	1	19	58	115	84	34	119	90	0	0	1	1	1	32	1.4	3	0	1	0	1	0	0	1
6d	0	59	78	97	42	70	111	77	0	0	1	1	1	30	0.6	5	0	0	1	1	1	0	1
100a	1	57	77	95	37	68	105	63	0	0	1	1	1	30	1.0	5	1	1	1	1	0	0	1
101b	0	40	67	97	42	52	107	68	0	0	1	1	1	29		3	1	0	1	1	1	0	1
101c	0	6	26	100	50	15	115	84	0	0	1	1	1	31		3	1	0	1	1	1	0	1
123a	0	18	54	109	73	21	91	27	0	0	1	1	1	31		0	1	0	0	1	1	0	0
90a	1	45	72	100	50	52	99	47	1	0	1	0	1	28	0.8	0	1	1	1	0	1	1	1
127a	1	38	69	105	63	55	118	88	0	0	1	0	1	26	1.0	3	0	0	1	1	1	0	1
120c	0	22	51	91	27	29	99	47	0	0	1	1	1	29		3	0	0	0	1	1	0	1
109b	0	30	58	95	37	31	93	32	0	0	0	1	1	30	1.2	1	1	1	1	1	1	0	1
110a	0	27	68	123	94	39	115	84	0	0	1	1	1	33	1.2	1	1	1	0	1	1	0	0
118h	0	25	64	117	87	33	100	50	0	0	1	1	1	28	1.0	2	1	0	1	0	1	0	1
126a	0	21	54	100	50	34	119	90	0	0	1	1	1	34	2.2	5	1	1	1	1	1	0	1

ID	Gender	AgeMo	PhyRS	PhySS	PhyPer	CogRS	CogSS	CogPer	Health	Develop	Surgery	Meds	EIService	AgeConcep	CreatPreg	Education	MedGroup	MedAza	MedAnti	MedMM	MedSir	MedPre	MedDBs
49c	1	33	65	107	68	44	113	81	0	0	0	1	1	39		5	0	0	0	1	1	0	1
127a	1	15	46	93	32	25	113	81	0	0	1	1	1	28	1.6	5	1	1	0	1	1	0	1
105a	0	35	68	107	68	51	117	87	0	0	1	1	1	37	1.0	1	1	0	1	1	1	1	1
132a	1	8	30	94	34	12	97	42	0	0	1	1	1	23	0.8	3	1	0	0	1	1	0	1
50a	1	60	82	99	47	70	100	50	0	0	1	1	0	35	1.3	2	0	0	1	1	1	0	1
100b	0	21	56	108	70	31	112	79	0	0	1	1	1	33	0.8	5	1	1	0	1	1	0	0
102a	1	31	68	115	84	46	117	87	0	0	1	1	1	30	1.5	5	1	0	1	1	1	0	1
139a	0	11	41	100	50	21	115	84	0	0	1	1	1	31	0.7	3	1	0	0	1	1	0	0
81b	1	62	40			50	78	7	1	1	0	0	0	32		3	1	0	1	1	1	0	1
82a	1	55	72	86	18	60	94	34	0	0	1	1	1	35	1.2	4	1	1	0	1	1	1	1
76a	1	60	74	86	18	65	95	37	0	0	1	1	1	32	1.2	3	1	0	0	1	1	0	1
113c	0	26	67	120	91	30	95	37	0	0	1	1	1	28	2.0	1	1	0	1	1	1	0	1
134b	1	52	81	106	66	66	111	77	0	0	1	1	1	36	1.1	2	1	0	1	1	1	0	1
122a	0	21	54	100	50	41	132	98	0	0	1	1	1	28	1.0	5	1	0	1	1	1	0	0
94b	1	38	72	113	81	48	107	68	0	0	1	1	1	32	1.0	2	1	0	1	1	1	0	0
98c	0	20	56	108	70	25	94	34	0	0	1	1	1	36	1.1	3	0	0	1	1	1	0	0
133a	1	28	48	80	9	28	87	19	0	0	0	1	1	29	0.96	5	1	0	1	0	1	0	0
115b	0	57	78	97	42	64	98	45	0	0	1	1	0	23	1.0	1	1	1	1	1	1	0	1
115c	1	25	58	100	50	31	97	42	0	0	1	1	1	25	1.0	1	1	1	1	1	1	0	1
139a	0	21	57	111	77	27	100	50	0	0	1	1	1	39	1.6	1	0	0	1	1	1	0	1
128a	0	17	60	122	93	30	117	87	0	0	1	1	1	34	1.1	2	1	0	0	1	1	0	1
79a	0	62	82	99	47	77	120	91	0	0	1	1	1	29	1.3	3	1	0	0	1	1	1	1
112a	0	28	68	119	90	36	101	53	0	0	1	1	1	20		2	1	0	0	0	1	1	1
137a	1	10	38	95	37	14	94	34	0	0	1	1	1	33	1.1	4	1	1	1	1	1	0	1
135a	0	37	67	100	50	49	108	70	0	0	1	1	1	32	1.3	1	0	0	0	1	1	0	1
62B	0	52	63	79	8	55	92	30	0	0	1	0	0	36	1.2	1	1	1	1	1	1	0	1
12b	0	13	51	115	84	23	115	84	0	0	1	1	1	27	1.3	2	0	0	0	1	1	0	0
107b	1	36	59	90	25	31	83	13	0	0	1	1	1	35	1.7	4	1	0	1	1	1	0	1

ID	Gender	AgeMo	PhyRS	PhySS	PhyPer	CogRS	CogSS	CogPer	Health	Develop	Surgery	Meds	EIService	AgeConcep	CreatPreg	Education	MedGroup	MedAza	MedAnti	MedMM	MedSir	MedPre	MedDBs
98a	1	34	68	107	68	59	130	98	0	0	1	1	1	37	3.3	3	1	1	0	1	1	0	1
53d	1	18	48	93	32	25	104	61	0	0	1	0	1	36	1.0	3	1	0	0	1	1	0	1
8c	1	50	84	113	81	67	113	81	0	0	0	1	1	30	0.8	0	0	1	0	1	1	0	1
106a	0	42	63	87	19	39	87	19	0	0	0	0	0	29	1.4	3	1	0	0	1	1	1	1
95a	1	38	64	94	34	48	107	68	0	0	1	1	1	34	1.0	3	1	0	0	1	1	1	1
13bI	0	4	21	103	58	9	107	68	0	0	1	1	1	37	0.6	3	0	1	1	1	1	1	1
11d	0	22	56	100	50	34	112	79	0	0	0	0	1	32	1.2	3	0	0	1	1	1	0	1
11c	0	56	75	92	30	60	94	34	0	0	0	0	0	30	1.2	3	0	0	0	1	1	0	1
119b	1	29	63	107	68	46	123	94	0	0	1	1	1	40	1.9	2	1	1	1	1	1	0	1
125a	1	21	54	100	50	34	119	90	0	0	1	1	1	20	1.1	2	1	1	1	0	1	0	1
116aI	0	30	60	99	47	30	91	27	0	0	1	1	1	24	1.4	2	1	1	0	1	1	0	1
116aII	0	30	58	95	37	30	91	27	0	0	1	1	0	24	1.4	2	1	1	0	1	1	0	1
130b	1	39	63	91	27	52	114	82	0	0	1	1	1	36	0.8	5	0	0	0	1	1	0	1
130a	0	59	82	104	61	60	94	34	0	0	1	1	0	34	0.8	5	0	0	0	1	1	0	1
118b	1	44	83	121	92	62	119	90	0	0	1	1	1	36	0.9	3	0	0	1	1	1	0	1
137a	0	35	63	100	50	48	112	79	0	0	1	1	1	33	0.9	5	0	0	1	1	1	0	1
77a	1	58	81	103	58	68	105	63	0	0	0	0	1	31	1.4	5	1	1	1	1	1	0	1