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Short communication

Response to immunization in children born to renal transplant recipients using immunosuppressive drugs during gestation

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ABSTRACT

The use of immunosuppressive drugs can impair vaccination responses. When used during pregnancy, they may interfere with the development of the fetus's immune system. However, little is known regarding their influence on infant's response to vaccinations.

Twenty-seven children born to renal transplant mothers (Tx) taking immunosuppressive drugs and 31 healthy children had the humoral immune response and reactogenicity to tetanus, *Haemophilus influenzae* type b (Hib) and 7 pneumococcal serotypes evaluated. The evolution of BCG vaccine scar was also registered. Antibodies were measured by ELISA. Lymphocyte immunophenotyping was performed on cord blood and at 7-8 months of age.

Among Tx neonates, 82.4% had low B lymphocyte numbers at birth, and 29.4% had also low numbers of other lymphocyte subpopulations. Nevertheless, all children developed protective antibodies with similar antibody concentrations to the control group. Vaccine reactogenicity was similar in both groups and BCG healing was uneventful.

1. Introduction

Solid organ transplant recipients need to maintain immunosuppressive drugs during pregnancy to preserve maternal health and the transplanted organ. However, these drugs cross the placenta and there is concern about the consequences for the fetus and the neonate [1]. Previous studies with a small number of infants have shown reduced numbers of B, CD4+ T or CD8+ T lymphocytes at birth, with return to normal levels during the first year of life [2–6].

Our group has recently shown that children born to renal transplant recipients evaluated at birth and at 8 months of age had significant differences in the number and expression of activation markers in cells from the immune system when compared to healthy children [7].

It is possible that these immune alterations interfere with vaccine immune responses. Another concern is regarding adverse events to live vaccines administered in the first months of life.

To our knowledge, there are no reports of prospective evaluation of vaccine responses in children born to solid organ transplant mothers who received immunosuppression during gestation compared to healthy children.

2. Materials and methods

This is a prospective study that took place from July 2009 to April 2013 comparing children born to renal transplant mothers exposed to immunosuppressive drugs during pregnancy with healthy children.

The transplant group was composed of children born to renal transplant mothers exposed to immunosuppressive drugs during gestation. The control group included healthy children not exposed to immunosuppressive drugs during gestation, born at term and adequate for gestational age. Exclusion criteria for control group were: children born to mothers with immunodeficiency, corioaminionitis, infections in the previous 7 days, use of antibiotics in the past 15 days, clinical or

Abbreviations: NK, natural killer; BCG, bacille Calmette–Guérin; DTP_w/Hib, combined diphtheria/tetanus/whole-cell pertussis and *Haemophilus influenzae* type b vaccine; IPV, inactivated trivalent poliovirus vaccine; PRPp, olyribosyl ribitol phosphate.

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serological evidence of congenital infections, hypertension and diabetes.

Written informed consent was obtained from parents before enrollment. This study was approved by the Ethics Committee of the Federal University of São Paulo, Brazil.

Children from both groups were followed up by the same pediatrician (MISD) for one year at monthly intervals during the first 6 months; after that, they were seen by the pediatrician on 3 other occasions during the second semester of life. If necessary, extra appointments were also programmed.

Vaccination schedule included intradermal BCG and hepatitis B at birth. Children born under 2 kg had BCG postponed until they reached that weight. At one month of age, infants received hepatitis B vaccine. At 2 and 4 months, combined diphtheria/tetanus/whole-cell pertussis and *Haemophilus influenzae* type b vaccine (DTP_w/Hib), conjugate pneumococcal vaccine, inactivate poliovirus vaccine (IPV), all intramuscularly and oral monovalent rotavirus vaccine. At 6 months, DTP_w/Hib, hepatitis B, IPV and conjugate pneumococcal vaccines. At 3 and 5 months, conjugate meningococcal C vaccine.

Parents were instructed to complete a diary for three days after vaccinations to record systemic reactions (fever, drowsiness, irritability, diarrhea, vomiting, unusual crying, loss of appetite) and local reactions (redness, swelling and pain) to DTPw/Hib, pneumococcal and IPV vaccines. The evolution of BCG were reported by parents and examined by the pediatrician at each visit.

Blood samples were collected from umbilical cord at birth and from a peripheral vein at 7–8 months of age into heparin tubes (BD Biosciences, Franklin Lakes, USA). At 7–8 months, part of the blood sample was centrifuged, aliquoted and plasma samples were stored at −80 °C until analysis.

Immune phenotypic analyses were performed on fresh blood as previously described from blood samples collected at birth and at 7–8 months of age [7]**.** CD3+, CD4+ and CD8+ T lymphocytes, B lymphocytes and NK cells per cubic millimeter were compared to normal Brazilian values [8].

Tetanus antibodies were measured by an in-house double-antigen ELISA as previously described [9]. Individuals with antibody concentrations ≥0.1 IU/mL were considered to be fully protected; individuals with levels <0.01 IU/mL were considered to be non-immune; those with antibodies ≥0.01 IU/mL and <0.1 IU/mL were classified as having basic immunity [10].

H. influenzae type b IgG antibodies were measured by indirect ELISA according to Madore et al.'s technique [11]. Anti-polyribosyl ribitol phosphate (PRP) Hib antibody concentrations >0.15 μg/mL were considered protective [12,13].

Streptococcus pneumoniae IgG antibodies were tested by ELISA in accordance with the World Health Organization's protocol [14]. Antibodies to seven *S. pneumoniae* serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) were tested. Individuals with antibody concentrations equal to or greater than 0.35 μg/mL were considered protected against invasive pneumococcal disease [15].

3. Results

From July 2009 to April 2013, 58 children were included in the protocol and followed up for 1 year. Twenty-seven were born to renal transplant women and 31, from healthy women.

Table 1
Clinical and demographic characteristics of mothers and neonates from transplant and control groups.

Parameters		Transplant $n=24$	Control $n=31$	P Value
Mothers				
Mean ± SD age at delivery in years (range)		28.6 ± 4.4 (17.3–35.9)	27.3 ± 6.7 (17.0–41.4)	0.044[a]
Hypertension before gestation		7 (29.2%)	0	na[b]
Hypertension during gestation		16 (66.7%)	0	na
Preeclampsia		14 (58.3%)	0	na
Gestational diabetes		2 (8.3%)	0	na
Urinary tract infection during gestation		17 (70.8%)	10 (32.3%)	0.005[c]
Antibiotic use during gestation		20 (83.3%)	13 (32.3%)	0.002[c]
Mean ± SD parity (range)		1.5 ± 0.9 (1–4)	1.7± 0.9 (1-4)	0.939[a]
Cause of renal dysfunction			–	–
Glomerulonephritis		10 (41.7%)	–	–
Hypertension		4 (16.7%)	–	–
Pyelonephritis/recurrent urinary tract infection		4 (16.7%)	–	–
Alport syndrome		1 (4.2%)	–	–
Systemic lupus erythematosus		1 (4.2%)	–	–
Indeterminate		4 (16.7%)	–	–
Immunosuppressive drugs: mean daily dose (range), users (%)			–	–
Azathioprine	100 mg (50–150)	24 (100%)	–	–
Prednisone	5.9 mg (5–10)	24 (100%)	–	–
Calcineurin inibitor				–
Tacrolimus	6.3 mg (3–12)	17 (70.8%)	–	–
Cyclosporine	161 mg (75–250)	7 (29.2%)	–	–
Mean ± SD time lag between transplantation and conception in years (range)		4.0 ± 3.0 (0.4–10.1)	–	–
Mean ± SD serum creatinine around delivery time (range)		1.35 ± 0.6 (0.67–2.88)	–	–
Neonates				
Cesarean delivery		18 (75.0%)	12 (38.7%)	0.013[c]
Female gender		11 (45.8%)	17 (54.8%)	0.591[c]
Mean ± SD birth weight in g (range)		2567 ± 610.8 (1330–3685)	3362 ± 261.7 (2800–3755)	0.001[a]
Mean ± SD length in cm (range)		45.8 ± 3.6 (36.5–51.0)	48.9 ± 1.6 (46.0–52.0)	0.003[a]
Mean ± SD 5th minute Apgar score (range)		9 ± 0.7 (7–10)	10 ± 0.5 (8–10)	0.987[a]
Mean ± SD gestational age in weeks (range)		37.2 ± 2.4 (31.3–41.0)	39.5 ± 0.9 (37.6–41.4)	<0.001[a]
Premature neonates		11 (45.8%)	0	na
Small for gestational age neonates		10 (41.7%)	0	na

SD: standard deviation,
[a] *t* test.
[b] na: not applicable.
[c] Chi-square test