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Maternally acquired IgG immunity in neonates born to renal transplanted women

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ABSTRACT

Neonates born to renal transplanted women are exposed in utero to immunosuppressors and to antenatal conditions that may predispose the neonate to a high risk of prematurity and intrauterine growth retardation. These factors might interfere with the transfer of maternal IgG immunity. Total IgG levels and specific antibodies to measles, varicella, tetanus, *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* (serotypes 4,6B,9V,14,18C,19F and 23F) were evaluated on maternal and cord blood samples of 23 sets of renal transplanted women and their newborns and 32 sets of healthy women-newborns at term. Total IgG levels were measured by nephelometry and specific antibodies, by ELISA. Renal transplanted mothers had lower median tetanus antibodies (0.67 IU/mL) than controls (1.53 IU/mL; $p = 0.017$). Neonates from renal transplanted mothers had lower median tetanus antibodies (0.95 IU/mL) than controls (1.97 IU/mL, $p = 0.008$). Antibodies to measles, varicella, Hib and the 7 serotypes of *S. pneumoniae* were similar between groups. Maternal antibodies were associated with an increase in neonatal antibodies for all antigens; gestational age was associated with an increase in Hib neonatal antibodies. Preeclampsia was associated with a decrease in neonatal total IgG and serotype 4 *S. pneumoniae* antibodies; chronic hypertension was associated with a decrease in neonatal serotype 6B *S. pneumoniae* antibodies. As neonates from transplanted women may be born with lower tetanus antibodies than controls, efforts should be made to keep maternal vaccines up-to-date. Clinical antenatal care with control of preeclampsia, chronic hypertension and prevention of premature delivery might also contribute to neonatal antibody levels to specific antigens at birth.

1. Introduction

Technological advances in the field of solid organ transplantation have allowed an increase in both the survival and the quality of life for transplanted individuals [1]. Women previously infertile can regain sexual activity and the ability to conceive and to carry pregnancy to term [2,3]. However, these women need immunosuppressive drugs for life to reduce the risk of organ rejection, even during gestation [4].

Pregnancy after renal transplantation may predispose the neonate to a higher risk of prematurity and intrauterine growth retardation [5]. Because these neonates are exposed to immunosuppressive drugs during their intrauterine life, they may be born with an altered immune system, what could represent an extra challenge to the known exposure to the extra-uterine environment [6].

Protection against infections during the period when the child is still unable to produce adequate amounts of its own antibodies is conferred mainly by maternal antibodies of immunoglobulin G (IgG) transferred across the placenta during gestation [7], which depends on maternal antibody levels [8]. Different immunologic and infectious conditions such as maternal hypergammaglobulinemia [9], maternal HIV infection [9], malaria placental infection [10,11] and prematurity [12] may impair transfer of antibodies from mother to fetus.

However, to the best of our knowledge, there is no published research on the transplacental antibody transfer to the fetus from solid organ transplanted pregnant women.

The aims of this study were to evaluate total IgG and antibodies to measles, varicella, tetanus, Hib and *Streptococcus pneumoniae*

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(serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) transferred transplacentally by renal transplanted mothers taking immunosuppressive drugs during gestation, and to compare them to sets of healthy mothers and their neonates born at term.

2. Methods

2.1. Subjects

Pregnant women previously submitted to kidney transplantation and their neonates conceived after transplantation were evaluated.

This study was approved by the Ethics Committee of the Federal University of São Paulo, in São Paulo, Brazil (0111/09). All participants gave written informed consent prior to enrolment in the study.

All women submitted to renal transplantation before gestation and followed at the obstetric outpatient clinic were eligible for enrollment in this study. Eligibility criteria for the control group were: pregnant women with negative serology for HIV, syphilis, hepatitis B and C during the antenatal care and their neonates born at term with adequate birth weight for gestational age.

Exclusion criteria for the control group were any maternal or neonatal clinical complications or suspicion of infection at birth.

Twenty-three sets of mothers previously submitted to kidney transplantation and their newborns (transplant group) and 32 sets of healthy mothers and full-term newborns (control group) were included. Pregnant women from transplant group were selected during antenatal care; pregnant women from control group were selected before delivery on hospital admission.

Data regarding maternal immunization were collected by vaccination card review. Also, maternal history of measles and varicella infection was investigated. Women without vaccination card were excluded from the vaccination analysis.

During the study period, the vaccination calendar of healthy pregnant women in Brazil included a tetanus–diphtheria (Td) vaccine booster for those who had received 3 doses in the past and had not had a Td dose in the previous 5 years; since 2010, influenza vaccine was also offered to all pregnant women during the influenza season. Pregnant women were then considered up-to-date for tetanus immunization if they had received primary vaccination schedule with 3 doses and a vaccine booster in the last five years [13].

Vaccination schedule from renal transplanted mothers was evaluated according to the recommendations of the Brazilian Ministry of Health [14] for recipients of solid organ transplants, and included the following vaccines: tetanus–diphtheria, Hib (for women under 19 years of age), 23-valent polysaccharide pneumococcus, hepatitis B, hepatitis A, influenza and poliomyelitis.

According to gestational age at birth, infants were considered preterm (<37 weeks), or term infants (>37 weeks) [15]. Gestational age was determined either by the best obstetric estimate or using the New Ballard or Capurro method.

2.2. Blood sample collection

Maternal peripheral blood and cord blood were collected at delivery from each mother–infant set into heparin tubes (BD Biosciences, San Jose, USA).

2.3. Detection of plasma total IgG and specific antibodies

Tetanus antibodies were measured by an in-house double-antigen ELISA as described by Kristiansen et al. [16]. Tetanus antibodies equal to or greater than 0.1 IU/mL were considered to be protective levels [17].

Measles IgG antibodies were measured by indirect ELISA as previously described [9]. Individuals with measles antibodies equal to or greater than 0.12 IU/mL [18] were considered to be protected.

Varicella IgG antibodies were measured by indirect ELISA as previously described by Ono et al. [19]. Individuals with varicella antibodies equal to or greater than 0.1 IU/mL [20] were considered to be protected.

Hib IgG antibodies were measured by indirect ELISA [21]. *Haemophilus influenzae* type b antibody titers considered protective were those above 1.0 μg/mL [22].

S. pneumoniae IgG antibodies were tested by ELISA [23]. Individuals with antibodies equal to or greater than 0.35 μg/mL were considered to be protected from invasive disease [24].

Plasma total IgG concentrations were assessed by laser nephelometry (Dade Behring Nephelometer II, Marburg, Germany) using specific kit from Dade Behring (Newark, USA).

2.4. Statistical analysis

Numerical unrelated variables were analyzed by Mann Whitney test. For categorical variables, Chi-Square (χ^2) test or Fisher's exact test were used. Univariate and multiple linear regression analyses were performed to determine factors associated with neonatal total IgG and specific antibodies. Level of significance was set at $p < 0.05$. Statistical analyses were performed using SPSS statistics version 17.0 (IBM, New York, USA).

3. Results

3.1. Characteristics of study groups

The characteristics of mothers and neonates are shown in Tables 1 and 2, respectively.

3.2. Antibody levels

Total IgG levels were lower in neonates from transplant group when compared with neonates from control group. Mothers and neonates from transplant group had lower tetanus antibody levels than mothers and neonates from control group (Table 3).

On the other hand, maternal antibody levels to measles, varicella, Hib and the seven *S. pneumoniae* serotypes assessed were similar between mothers and between neonates from transplant and control groups. Maternal IgG concentrations were also similar between mothers from both groups (Table 3).

Transplant group showed a lower percentage of mothers (81.8%) with protective antibodies to tetanus when compared to control group (100.0%) (Fisher's exact test, $p = 0.026$). The same was observed for neonates (transplant group, 81.8% and control group, 100.0%; Fisher's exact test, $p = 0.026$).

By contrast, there was no difference in the percentage of mothers with protective antibody levels to measles, varicella, Hib and the seven *S. pneumoniae* serotypes between transplant and control groups (measles, 90.5% versus 96.9%, $p = 0.565$; varicella, both groups 100.0%, Fisher's exact test, $p > 0.999$; Hib, 26.1% versus 43.8%, Fisher's exact test, $p = 0.257$; *S. pneumoniae*, both groups 100.0% for all serotypes, Fisher's exact test, $p > 0.999$). The same was observed between neonates (transplant versus control group: measles, 90.5% versus 100.0%, Fisher's exact test, $p = 0.170$; varicella, both groups 100.0%, Fisher's exact test, $p > 0.999$; Hib, 13.0% versus 31.3%, Fisher's exact test, $p = 0.197$; *S. pneumoniae*, both groups 100.0% for all serotypes, Fisher's exact test, $p > 0.999$).