ORIGINAL ARTICLE

Neonatal infection and passive acquisition of serum total IgG and reactive with "Streptococcus" B, anti-LPS of "Klebsiella spp" and "Pseudomonas spp" antibodies in twins

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SUMMARY

OBJECTIVE: *To describe the concentration of total and specific IgG antibodies anti-Streptococcus B, anti-lipopolysaccharide of Klebsiella spp, and anti-lipopolysaccharide of Pseudomonas spp in the umbilical cord of newborn(NB) twins and to analyze the association between neonatal infection and antibody concentration in the umbilical cord blood.*

METHODS: *A prospective cross-sectional study of a cohort of NB twins admitted during the period of 20 months. Patients with malformations and mothers with infection were excluded. Variables analyzed: gestational age(GA); birth weight(BW); antibody concentrations in umbilical cord blood; infection episodes. We used the paired Student t-test, Spearman correlation, and generalized estimation equation.*

RESULTS: *57 pairs of twins were included, 4 excluded, making the sample of 110 newborns. GA=36±1.65weeks and BW=2304.8±460g(mean±SD). Antibody concentrations in twins(mean±SD): total IgG=835.71±190.73mg/dL, anti-StreptococcusB IgG=250.66±295.1 AU/mL, anti-lipopolysaccharide of Pseudomonas spp IgG=280.04±498.66 AU/mL and anti-lipopolysaccharide of Klebsiella spp IgG=504.75±933.93 AU/mL. There was a positive correlation between maternal antibody levels and those observed in newborns(p <0.005). The transplacental transfer of maternal total IgG and anti-LPS Pseudomonas IgG antibodies was significantly lower at NB GA <34 weeks(p <0.05). Five newborns were diagnosed with an infection. Infants with infection had significantly lower total IgG concentration(p <0.05).*

CONCLUSION: *This study showed a positive correlation between maternal and newborn antibodies levels. In infants younger than 34 weeks there is less transfer of total IgG and anti-LPS Pseudomonas IgG. The highest incidence of infection in the newborn group who had significantly lower total IgG serum antibodies reinforces the importance of anti-infectious protection afforded by passive immunity transferred from the mother.*

KEYWORDS: *Infant, newborn. Twins. Maternal-fetal exchange. Immunoglobulin G. Klebsiella. Pseudomonas. Streptococcus.*

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INTRODUCTION

Over the last decades, the incidence of twin pregnancy has increased due to the use of assisted reproduction techniques and the choice of women to have children later in life. Twin pregnancy presents an additional risk of complications for the fetus, newborn, and mother. In comparison with singleton pregnancies, there is a greater risk of congenital malformation, intrauterine growth restriction, cerebral palsy, infection, mortality, and prematurity; the rate of prematurity is approximately 60% in this population[1].

The neonatal immune system has some special features necessary for the period of transition from the intrauterine to the extrauterine environment. Fetuses and neonates have limited antigenic exposure to induce adaptive immunity. The immunocompetence of newborns progresses rapidly in the first three months of life, with the maturation of the cells involved in the adaptive response and acquired antigenic experience[2]. Newborns need to be able to initiate an efficient inflammatory response to ensure protection against infections and, at the same time, allow for their colonization to happen without exacerbated inflammation in response to it. Innate immunity is modulated, with a relative decrease of the *T helper* type 1 (Th1) proinflammatory response and polarization of the *T helper* type 2 (Th2) anti-inflammatory response, which leads to greater susceptibility to infection by intracellular pathogens and lower response to vaccines. Therefore, at the beginning of life, newborns depend on the components of innate response and passive acquisition of antibodies from the mother[3,4].

Epidemiological studies have shown an increased incidence of neonatal sepsis by gram-negative agents such as *Klebsiella* and *Pseudomonas* after the introduction of the recommendation of intrapartum prophylaxis for pregnant women colonized by *Streptococcus* B[5-7].

The objective of this study is to describe the total concentrations of IgG antibodies e specific concentration of anti-*Streptococcus* B, anti-lipopolysaccharides of *Klebsiella* and *Pseudomonas* in the umbilical cord of twins and analyze the possible association between the concentrations of these antibodies and the occurrence of infection.

METHODS

This is a prospective cross-sectional study of a cohort of newborns from twin pregnancies followed-up for 20 months. We excluded newborns with malformation, congenital or maternal infection, and amniorrhexis for more than 12 hours.

The following variables were analyzed: gestational age (GA); birth weight (BW); concentration of antibodies and episodes of infection.

The study was approved by the Research Ethics Committee of the institution. Blood samples from the umbilical cords were collected after a free and informed consent form was signed by the parents. The blood was placed in a tube containing separator gel (BD Vacutainer SST) and sent to the laboratory, where it was centrifuged at 2000 rpm for 10 minutes at 4°C. The sera were divided and stored at -80°C.

The total serum concentrations of IgG antibodies were assessed by nephelometry, using a nephelometer (Behringer, USA) with appropriate standards and controls. The dosages of immunoglobulins and serum dilution of the samples were performed according to the assay protocol a Behringer nephelometer. We used a strain of *Streptococcus sp* from group B type III number H36C, batch 05/85, and lipopolysaccharides of *Klebsiella spp* (L-4268, Sigma, USA), and *Pseudomonas spp* (L-9143, Sigma, USA), both isolated from patients with hospital infections. The IgG antibodies anti-*Streptococcus* B, anti-LPS of *Klebsiella,* and anti-LPS of *Pseudomonas* were analyzed by enzyme-linked immunosorbent assay (ELISA).

To describe the results, we used the relative (percentages) and absolute (n) frequencies of the classes of each qualitative variable. For the quantitative variables, we used the mean, median, minimum value, maximum value, and standard deviation to indicate data variability.

The comparison between birth weight and concentration of antibodies in the umbilical cord blood was done using the paired Student's t-test or the paired Wilcoxon test, and the Mann-Whitney test. The same analyses were carried out between twins with and without infection.

We calculated the Spearman correlations between the levels of maternal and NB antibodies to assess the existence of correlations.

To evaluate neonatal antibodies according to the presence of infection and gestational age, we described the concentrations of antibodies per categories of interest and compared to the values of IgG between the categories, with the use of generalized estimation equations (GEE) with normal marginal distribution and identity function, assuming a symmetrical

component correlation matrix between twins and other antibodies with use of generalized estimation equations with gamma marginal distribution and identity function, assuming a symmetrical component correlation matrix between the twins.

The tests were conducted with a significance level of 5%. The software used for analysis was SPSS and MS Office Excel for Windows.

RESULTS

We studied 59 pairs of twins; four pairs were excluded, three due to insufficient collection of material, and one due to congenital malformation (tetralogy of Fallot). We included 55 pairs of twins, which comprised a sample of 110 newborns.

The most frequent type of delivery was by cesarean section (86%). The maternal age was 29.4 ± 5.9 years (mean ± SD), gestational age was 36 ± 1.65 weeks (mean ± SD) and the birth weight was 2304,8 ± 460g (mean ± SD). The gestational age ranged from 29 to 38 weeks. Most of the newborns presented a gestational age from 34 and 36 6/7 weeks (50.9%), appropriate classification for the gestational age (80.7%), and birth weight between 1500 and 2499g (57%). There was a slight predominance of females (52.7%).

In all serum samples of mothers and their NBs, we detected the total IgG antibodies and specific antibodies anti-GBS, anti-LPS of *Klebsiella*, and anti-LPS of *Pseudomonas*. The antibody concentrations found in 55 mothers and 110 newborns are presented below (mean±SD): Total IgG Mother 830.25±204.47 mg/dL and total IgG NB 835.71±190.73 mg/dL; IgG anti-*Streptococcus* B Mother 438.37±417.24 AU/mL and IgG anti-*Streptococcus* B NB 295.10±250.66 AU/mL; IgG anti-LPS *Pseudomonas* Mother 337.26±694.52 AU/mL and IgG anti-LPS *Pseudomonas* NB 280.04 ± 498.66 AU/mL and IgG anti-LPS *Klebsiella* Mother 715.5±1212,9 AU/mL and IgG anti-LPS *Klebsiella* NB 504.75±933.93 AU/mL.

There was a positive correlation between the levels of maternal antibodies and those in the newborns ($p<0.005$), as shown in Table 1.

The transplacental transfer of maternal antibodies IgG total and IgG anti-LPS *Pseudomonas* was significantly lower in NB with GA < 34 weeks ($p<0.05$). For the serum antibodies of the IgG anti-EGB and anti-LPS of *Klebsiella* class, no difference was observed between the groups. These data are presented in Table 2.

TABLE 1. CORRELATION BETWEEN THE CONCENTRATIONS OF SERUM ANTIBODIES OF THE TOTAL IGG CLASS AND SPECIFIC OF MOTHERS AND NEWBORNS

Variable	NB 1			NB 2		
	Correlation	N	p	Correlation	N	P
IgG Mother (mg/dL)	0.371	55	0.005	0.416	55	0.002
Anti-GBS Mother (Ua/mL)	0.855	55	<0.001	0.925	55	<0.001
Anti-Klebsiella Mother (Ua/mL)	0.895	55	<0.001	0.911	55	<0.001
Anti-Pseudomonas Mother (Ua/mL)	0.954	55	<0.001	0.946	55	<0.001

Results of the Spearman correlation

TABLE 2. CORRELATION BETWEEN THE CONCENTRATIONS OF SERUM ANTIBODIES OF THE TOTAL IGG CLASS AND SPECIFIC OF MOTHERS AND NEWBORNS ACCORDING TO THE GESTATIONAL AGE

Variable	Gestational age (sem)	Average	SD	Median	Minimum	Maximum	N	P
IgG NB (mg/dL)	≥ 34 < 34	851.1 639.4	181.6 207.6	842.5 712.0	273 273	1352 847	100 10	0.013*
Anti-Streptococcus NB (Ua/mL)	≥ 34 < 34	296.0 283.2	256.6 168.1	199.3 214.9	34.6 108.3	1313.8 514.1	100 10	0.918
Anti-Klebsiella NB (Ua/mL)	≥ 34 < 34	527.3 216.9	963.1 309.4	213.5 100.4	13.1 26.7	6205.4 956.9	100 10	0.183
Anti-Pseudomonas NB (Ua/mL)	≥ 34 < 34	295.3 85.1	514.8 27	103.8 87.8	13.3 47.1	3567.8 119.3	100 10	0.032

Results of the Mann-Whitney test; * Results of the Student's t-test

There were five (4.5%) diagnosed cases of infection (late sepsis) with positive blood culture during their hospitalization. The etiologic agents identified in the blood cultures were *Staphylococcus epidermidis*, *Klebsiella sp*, *Acinetobacter baumanni,* and *Staphylococcus aureus*. As for the outcome in the infection group, four NB were discharged from the hospital and one NB evolved to death.

Table 3 shows that the concentration of total IgG antibodies was significantly lower in newborns who presented infections when compared to those without infections (p=0.049). Regarding the specific IgG antibodies, no significant difference was observed between the newborns with and without neonatal sepsis.

DISCUSSION

To our knowledge, this is the first study in Brasil to analyze the transplacental transfer of antibodies in twin newborns and the rate of infection. Stach et al.[8,9] analyzed the transplacental transfer of antibodies in twins according to maternal pathologies, gestational age, chorionicity, changes in the pulsatility of the umbilical artery, placental weight, and restriction of growth. The present study prospectively followed this cohort of newborns and their evolution during hospitalization. We observed that in all serum samples of mothers and their NBs, we detected total IgG antibodies and specific antibodies anti-GBS, anti-LPS of *Klebsiella*, and anti-LPS of *Pseudomonas*. This finding confirms the transplacental transfer of these antibodies, as previously demonstrated by other authors[8,9].

We observed a positive correlation ($r > 0.8$ and $p < 0.05$) between the concentrations of serum total IgG antibodies and the specific antibodies anti-GBS, anti-LPS of *Klebsiella*, and anti-LPS *Pseudomonas* in mothers and NB. These findings are in line with those in the literature; maternal IgG is actively transferred to the fetus via endocytosis. This process is mediated by the neonatal Fc receptor (FcRn) and the pH of the medium[10]. The more acid the pH of the medium, the greater the affinity of IgG with the FcRn. The IgG molecule from the maternal circulation binds to the FcRn receptor in the syncytiotrophoblast and is internalized in a endosome. To ensure a high affinity between the FcRn receptor and the IgG molecule, and protection against the action of lysosomal enzymes, the endosome is acidified. When the gallbladder reaches the fetal circulation, it finds a physiological pH and releases the IgG molecule to the fetus[10-12].

In 10 NB (8.7%) whose gestational age was less than 34 weeks, the average concentration of total serum IgG antibodies (p=0.013) and IgG anti-LPS *Pseudomonas* (p=0.032) was significantly lower. This behavior was expected since the transplacental transfer of antibodies is influenced by the concentration of maternal immunoglobulin, class and subclass of antibody, and gestational age. The transplacental transfer of antibodies begins around 13 weeks and increases until the third quarter[10-12]. Malek et al.[13] found an average increase in the concentration of total serum IgG antibodies from 1.4± 0.7 g/L at 17-22 weeks(10% of the maternal concentration) to 5.6±1.1 g/L at 28-32 weeks (50% of the maternal concentration). This increase in the antibody transfer continues in the third quarter, with a concentration of fetal IgG greater than the maternal by the end of the gestation[10-14]. Brasil et al.[15] studied the transplacental transfer of total IgG and IgG anti-*Streptococcus* B and demonstrated that it is less efficient in premature NB. The positive correlation between the positive concentration and serum concentration of total IgG and IgG anti-*Streptococcus* B and gestational age proves the importance of prematurity as a determinant factor of low serum concentrations of these components in the immune repertoire of NB. Silveira-Lessa et al.[16] studied the passive acquisition

TABLE 3. CONCENTRATIONS OF ANTIBODIES IN THE NB ACCORDING TO THE PRESENCE OF INFECTION AND RESULTS OF THE COMPARATIVE TESTS

Variable	Infection	Average	Median	Minimum	Maximum	SD	N	P
Total IgG RN (mg/dL)	No Yes	849.1 554.8	831 615	273 273	1352 847	178.9 236.8	105 5	0.049*
IgG anti-Streptococcus NB (Ua/mL)	No Yes	298.0 234.8	200.8 190.3	34.6 122	1313.8 438.7	255.1 121.4	105 5	0.654
IgG anti-Klebsiella NB (Ua/mL)	No Yes	519.2 201.3	186.4 170.6	13.1 87.8	6205.4 329.3	953.4 110.6	105 5	0.952
IgG anti- Pseudomonas NB (Ua/mL)	No Yes	290.1 68.1	103.2 64.3	13.3 23.1	3567.8 107	508.3 32.2	105 5	0.447

Results of the EEG with gamma distribution; * Results of the EEG with normal distribution

in term and premature NB of IgG antibodies reactive with lipopolysaccharides of enterobacteria in neonatal infections. The levels of IgG anti-LPS *Klebsiella* and *E.coli* O26, O111, and O6 in premature NB were significantly lower when compared to their mothers. The transfer rates were lower in the group with a gestational age of fewer than 33 weeks (except for *E.coli* O26) and in preterm infants between 33 and 36 6/7 weeks of gestation (except for *Klebsiella* and *E.coli* O111) when compared to term NB. In the present study, regarding the serum antibodies of the IgG anti-EGB and anti-LPS *Klebsiella* class, no statistical difference was observed based on gestational age. This finding is likely due to the smaller number of cases in the group with a gestational age of fewer than 34 weeks.

In the present study, there were five (4.5%) diagnosed cases of infection with positive blood culture during their hospitalization. The concentration of the total IgG antibodies class was significantly lower in NB who presented infections when compared to those without infections (p=0.049). This result was expected, since IgG is the class of immunoglobulins with the highest concentration in the blood, with the role of bacteria opsonization and virus neutralization of[17]. The important role of IgG in immunity can be clinically exemplified by patients who present hypogammaglobulinemia and recurrent infections[18].

Epidemiological studies have documented that maternal antibodies alter the incidence and severity of infections[19]. Lin et al.[20,21] showed that newborns of mothers with concentrations of antibodies anti-*Streptococcus* B serotype Ia greater than 5 µg/mL had 88% less risk of developing sepsis caused by this bacterium in comparison with those of mothers with levels of antibodies anti-*Streptococcus*B serotype Ia less than 0.5 µg/mL. The authors also observed that children of mothers with higher levels of antibodies anti-*Streptococcus* B serotype III above 10 µg/mL had 91% less risk of developing sepsis caused by this bacterium in comparison with the children of mothers with levels of antibodies anti-*Streptococcus* B serotype III below 2 µg/mL. Similar results were found by Baker et al.[22] between the concentration of maternal antibody and relative risk of infection for early sepsis by *Streptococcus* B. The authors demonstrated that the children of mothers with a concentration of anti-*Streptococcus* B Ia, III, V antibodies greater or equal to 1.0 µg/mL had 70% less chance of developing sepsis by this agent. Larsson et al.[23] also found an association between the concentration of antibodies and infection. The authors demonstrated that there is a transplacental transfer of antibodies reactive with proteins and Rib (capsular protein of *Streptococcus* B) and that low concentrations of these antibodies are associated with invasive infection by *Streptococcus* B that express these proteins.

The pair of twins with the lowest gestational age (29 weeks) presented infection by *Acinetobacter baumani* and *Staphylococcus aureus*, respectively, and the second twin died. Although the passive acquisition of antibodies against these agents was not the object of this study, it is likely that the transfer of antibodies to the fetus was greatly reduced during the time of pregnancy. Considering the great vulnerability of preterm infants to infection[24,25], it is essential to know specifically how the transplacental transfer of antibodies occurs in relation to the most frequent bacteria in neonatal sepsis.

Among the limitations of this study, we emphasize the small number of NB with infections confirmed by blood culture. In the face of the results obtained, future studies with larger samples of NB twin and stratification of the groups for analysis according to gestational age are recommended.

CONCLUSION

We demonstrated a linear correlation between the levels of antibodies of mothers and newborns, proving that the total IgG antibodies and specific antibodies anti-*Streptococcus* B, anti-LPS of *Klebsiella*, and anti-LPS of *Pseudomonas* are transferred across the placenta barrier.

In newborns younger than 34 weeks, there was a lower transfer of total IgG and IgG anti-LPS *Pseudomonas*. The association between lower gestational age and decreased levels of anti-LPS of *Pseudomonas* antibodies confirms the greater vulnerability of these neonates to infection by this bacterium.

In preterm NB with infections, the total IgG concentration was significantly lower, which demonstrates the greater vulnerability and risk of infection in this population and the importance of passive immunity transferred through the placenta.

RESUMO

OBJETIVOS: *Descrever o título de anticorpos IgG total e específico anti-Streptococcus B, anti-lipopolissacarídeos(LPS) de Klebsiella e Pseudomonas no cordão umbilical em gêmeos e analisar a possível associação entre os títulos desses anticorpos e a ocorrência de infecção.*

MÉTODOS: *Estudo prospectivo transversal de uma coorte de recém-nascidos (RN) gemelares em 20 meses. Excluídos: malformação, infecção congênita ou materna. Variáveis estudadas: idade gestacional(IG); peso de nascimento(PN); título de anticorpos e episódios de infecção. Foram utilizados testes t-Student pareado, correlação de Spearman e equações de estimação generalizadas.*

RESULTADOS: *Elegíveis 59 pares de gêmeos, excluídos 4 e incluídos 55 pares (n=110RN). A IG foi 36±1,65semanas e o PN foi 2304,8±460g (média±DP). Concentrações de anticorpos dos RN(média±DP): IgG total=835,71±190,73 mg/dL, IgG anti-Streptococcus B=295,1±250,66 UA/mL, IgG anti-LPS Pseudomonas=280,04±498,66 UA/mL e IgG anti-LPS Klebsiella=504,75± 933,93UA/mL. Houve correlação positiva entre níveis de anticorpos maternos e aqueles observados nos RN (p<0,005). A transferência transplacentária de anticorpos maternos IgG total e IgG anti-LPS Pseudomonas foi significativamente menor em RN IG < 34semanas (p<0,05). Foram diagnosticados 5 RN com infecção. Os RN que apresentaram infecção tinham concentração de IgG total significativamente menor (p<0,05).*

CONCLUSÕES: *Na população estudada existe correlação entre os anticorpos maternos e os níveis de anticorpos no RN. Nos gêmeos menores que 34 semanas há menor transferência de IgG total e IgG anti-LPS Pseudomonas. Nos RN com infecção a concentração de IgG total é significativamente menor, o que demonstra a maior vulnerabilidade e risco de infecção dessa população e a importância da imunidade passiva transferida pela placenta.*

PALAVRAS-CHAVE: *Recém-nascido. Gêmeos. Troca materno-fetal. Imunoglobulina G. Klebsiella. Pseudomonas. Streptococcus.*

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