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Expression of FcRn receptor in placental tissue and its relationship with IgG levels in term and pre-term newborns

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Abstract

Problem—IgG is the only antibody class that is actively transferred from the mother to the fetus across the placenta by an active, neonatal Fc receptor (FcRn) mediated process during pregnancy, conferring passive immunity and protection against infections to the newborn during the first months of life. Preterm infants may not receive sufficient titers of protective antibodies, as most of them are transferred only after the 34th week of gestation. Because of the great importance of this process, we investigated in a clinical setting the placental transmission of IgG antibodies in term and preterm newborns.

Method of Study—This work was conducted in 85 woman and their newborns, divided into four groups according to their clinical gestational age (< 37 weeks were considered as preterm). Blood samples were collected from the mothers and their newborns' umbilical cords to analyze total serum IgG concentrations, and a subgroup of 32 placentas were analyzed by immunohistochemistry to quantify the expression of the FcRn receptor.

Results—Total IgG levels in both mothers and neonates increased significantly through the third trimester of gestation. Regarding the newborns, in all groups IgG levels exceeded their mother's values by a ~2.4%. A higher expression of FcRn was detected in placentas from newborns at week 36 of gestation onwards.

Conclusions—Our results obtained from clinical samples, were in line with previous descriptions in model systems and confirmed that the IgG transfer from maternal serum to the fetus is positively correlated with FcRn expression in placental tissue throughout gestation.

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Keywords

neonates; FcRn; placenta; IgG; preterm

1. INTRODUCTION

Protection against pathogens is achieved through the coordinated actions of the innate and the adaptive arms of the immune system. Newborns rely heavily on their innate immune defenses as their “educated” adaptive immunity fully develops only later, in the early years of life¹. Of the five antibody classes, IgG is the most prevalent in serum and certain mucosal tissues such as the airways, distal gastrointestinal tract and genitourinary tract, and has long been known to be the only class that is actively transferred from the mother to the fetus across the placenta by an active, neonatal Fc receptor (FcRn) mediated process during pregnancy, thus conferring short-term passive immunity and protection against infections to the newborn during the first months of life^{2,3,4}. Indeed, at the 32nd week of gestation, detectable IgG levels in newborns are only ~400 mg/dL (reference values for adults is 548–1768 mg/dL and in term newborns is 631–1431 mg/dL). Therefore, preterm infants may not receive sufficient titers of protective antibodies, as most of them are transferred only after the 34th week of gestation⁵.

Neonates are one of the highest risk age groups for mortality and morbidity from infection. According to the World Health Organization, 3.7 million neonates less than 28 days of age died in 2010 — 37% of these deaths were due to infectious causes⁶. Eleven percent of all infants are born premature, representing about 12.9 million infants born prematurely each year worldwide, a population exposed undoubtedly to a higher risk of death⁷.

FcRn is expressed mainly in the syncytiotrophoblast, where it transports IgG from the maternal circulation to the fetal capillaries of the placental villi by bidirectional transcytosis across a polarized cell layer^{8,9,10}. The syncytiotrophoblast internalizes fluid containing maternal IgG into endosomes, which are then gradually acidified thereby allowing IgG to bind tightly to the FcRn in a strictly pH-dependent manner and in a 2:1 stoichiometry^{2,3,11,12}. The endosome then fuses with the membrane on the fetal side of the syncytiotrophoblast, where the physiological pH promotes the dissociation of IgG from FcRn releasing the antibody to the fetal circulation. The FcRn molecule may then be recycled to the maternal membrane to perform additional rounds of transcytosis¹³. Therefore, the pH-dependent binding of IgG to FcRn allows for IgG transport through a cell layer and down a concentration gradient of IgG¹⁴.

In humans, the active role of this receptor starts early in fetal development and increases progressively from the early second trimester until the end of pregnancy⁵. Because of the great importance of acquiring maternal antibodies that can provide protection early in life, investigations into the mechanisms behind this pattern have been reported several times since the early 1980s. However, partly because of the very limited access to fetal samples (blood/placenta) in the first and second trimester, the vast majority of these reports were detailed reviews about the chemistry and functional physiology of the FcRn receptor, or studies using the ex-vivo placental transfer model, but that were not verified in human

clinical samples¹⁵. In fact, there are only limited number of reports of FcRn expression in early human life but have not been correlated with IgG levels¹⁶.

We now report on the placental transmission of IgG antibodies in clinical samples. Our specific objectives were to: 1) investigate if there is a relationship between maternal and the neonatal IgG levels, and 2) compare serum IgG levels and FcRn expression in placental tissue in preterm and term neonates according to gestational age (third trimester of pregnancy).

2. MATERIALS AND METHODS

2.1 Patients

The present work was conducted in 85 woman between 19 and 40 years of age and their 90 offspring (10 twins), admitted to the Obstetrics Department at the Clínica Universitaria Reina Fabiola, Córdoba, Argentina, between April and October 2013. All women that agreed to participate in this study signed an informed consent. Patients presenting prenatal diagnosis of placental pathology, immunological deficiencies or autoimmunity were excluded from the study as were newborns presenting any genetic syndrome diseases.

The mothers and their respective newborns were divided into four groups according to their clinical gestational age as determined by the Capurro method¹⁷: Group I, 32–33 weeks (n=8), Group II, 34–35 weeks (n=15), Group III, 36–37 weeks (n=9) and Group IV, 38–41 weeks (n=58). Those infants with gestational ages \leq 37 weeks were considered as preterm¹⁸.

2.2 Serum IgG levels determination

Immediately after birth, blood samples were collected from the mothers and their respective newborns' umbilical cords. The samples were centrifuged at 3000 rpm for 10 min and stored at -20°C until assayed. Total serum IgG concentrations (mg/dL) were measured by the quantitative radial immunodiffusion technique, using a commercial kit with anti-human IgG antibody (Diffuplate, Biocientífica SA, Buenos Aires, Argentina). Briefly, 3 μl of sera were incubated at 4°C for 48 hours in a humidified chamber to allow diffusion of the immunoglobulin. Following incubation, diameters of the precipitation rings of antigen-antibody complexes were measured and the concentration of IgG was calculated by generating a dose-response curve against a reference serum of pre-determined IgG concentration¹⁹.

2.3 Placental FcRn receptor

The placentas were obtained after birth and immediately fixed using a 10% buffered formaldehyde solution until further processing. Some placentas were lost during the process because of technical problems during urgency of a preterm delivery. Therefore, a subgroup of 31 placentas was analyzed.

To quantify the expression of the FcRn receptor, the placental tissue was mounted on positively charged slides and stained with the EnVision G2 Doublestain System, rabbit/mouse (DAB+/Permanent Red) Kit from Dako, following heat-induced epitope retrieval in antigen retrieval buffer (10 mM citrate, 1 mM EDTA, 0.05% Tween-20, pH 6.0). Slides were

stained with anti-hFCGRT (HPA012122, Sigma Aldrich) at 1/50 dilution overnight at 4°C. Initially, a counterstain was also used (hemotoxilin) in the slides; however, because the counterstain was observed to interfere with the DAB reaction when analyzing the images, its use was eliminated from the process.

For the quantification of the placental area expressing FcRn, digital pictures were taken using an Olympus optical microscope under a 20× magnification. Two pictures were taken from each slide in representative parts of the tissue and analyzed using the Image J software (W. Rastband, Research Services Branch, National Institute of Mental Health, Bethesda, MD, USA). The images were adjusted by brightness and saturation before using the “analyze particles” tool (Figure 1). The results were expressed as percentage of the total area expressing the receptor.

2.4 Ethical approval

This research protocol was approved by the Institutional Ethics Committee of the Clínica Universitaria Reina Fabiola, Facultad de Ciencias de la Salud, Universidad Católica de Córdoba, Argentina, and in accordance to the guidelines of the Helsinki Declaration, the Administración Nacional de Medicamentos Alimentos y Tecnología Médica Good Clinical Practices and in agreement with the Province of Córdoba (Argentina) laws for Research in humans (9694/09). Informed consent for all interventions and the use of data was acquired from all patients, and confidentiality is guaranteed under national laws for the protection of personal data (25326/00). The authors declare that there are no conflicts of interest.

2.5 Data analysis

Data analysis was performed using the Infostat statistical software (2013 version)²⁰. Values were expressed as median and range (Q1–Q3). To check the assumptions of normality and variance homogeneity, diagnostic techniques based in the residuals were applied. Accordingly, the data was analyzed using the Wilcoxon Mann–Whitney test or Kruskal–Wallis test and Dunn’s post-hoc test for multiple comparisons. In the case of categorical variables, the Chi Square test was applied. The significance level for all statistical tests was set at 0.05.

3. RESULTS

A total of 85 blood samples were obtained from the mothers, and 90 samples were obtained from the newborns umbilical cord. All newborns had a gestational age greater than 32 weeks; ten newborns (11.1%) were twins, 41 (45.6%) were born from primiparous mothers and 49 (54.4%) from multiparous mothers. The full clinical and biochemical data from maternal and cord blood IgG levels in the four groups are shown in Table 1.

The total IgG levels in both mothers and neonates were found to be within the normal range as published in the literature.

In the mothers, a slight increase in IgG levels was observed towards the end of gestation, reaching significantly higher levels in Group IV (38–41 weeks of gestation; $p < 0.0001$; Table 1); additionally a linear regression analysis of the data also showed a positive and significant

correlation between increased IgG levels and gestational age ($p < 0.001$; slope: 2.38; $r^2 = 0.21$).

No significant differences were found when analyzing the influence of the mothers' age or number of previous gestations on maternal IgG levels ($p = 0.85$ and 0.07 respectively).

In the newborns, the pre-term groups (I, II and III) showed a significantly lower IgG level than those individuals born at full term ($p < 0.0001$; Table 1). IgG levels increased by 2.44 mg/dL per week throughout gestation.

With respect to the impact of the newborn weight at birth, a regression analysis revealed that IgG levels increased significantly by 0.014 mg/dL per gram of body weight during the third trimester of gestation ($p < 0.001$; Figure 2).

Neither sex of the individual, age of the mother, or number of previous gestations influenced the newborns' IgG levels ($p = 0.98$; $p = 0.53$ and $p = 0.47$ respectively).

The total IgG levels detected in the newborns correlated with their mothers IgG levels, increasing progressively by 0.40 mg/dl for every 1.0 mg/dl of increase in the mother, and reached a significantly higher value towards the end of gestation in week 38 (Group IV) ($p < 0.0001$; Figure 3). Finally, IgG levels were significantly higher in the newborns than in their mothers in all four groups studied ($p < 0.05$, Table 1).

A total of 32 placental tissue samples were analyzed for the expression of FcRn (Group I $n = 1$; Group II $n = 8$; Group III $n = 5$; Group IV $n = 18$). When analyzing the percentage of the total area of the placental tissue expressing FcRn, we observed higher expression of the receptor in placentas obtained from term vs. preterm newborns (3.25% (2.8–3.6) ($n = 18$) vs. 2.69% (2.4–3.0) ($n = 14$), respectively, $p = 0.01$). In a further analysis, we observed that expression of the receptor increased significantly from week 36 of gestation onwards (Groups III and IV, $p = 0.004$, Figure 4).

Finally, an increase in the area of placental tissue expressing FcRn was associated with an increase in IgG levels in the newborns ($p < 0.0053$; slope = 0.02; $r^2 = 0.24$) (Figure 5).

4. DISCUSSION

Newborns, especially preterm infants, have an immature immune system that makes them a vulnerable population with high infection-associated morbidities and mortality rates^{21,22}. Premature neonates are even more susceptible to infections due to several factors, including immature mechanical barriers, limited neutrophils function, low plasma concentrations of specific antibodies, low activities of the complement system proteins and poor cooperation between T and B lymphocytes. This favors bacterial translocation across the intestinal epithelium and dissemination to other organs and tissues, thereby increasing the risk of systemic infections and potential for sepsis^{23,24,25}.

As previously mentioned, the immunoglobulins of the fetus consist almost entirely of maternal immunoglobulin G (IgG) transferred across the placenta. Such transplacental

transfer of immunoglobulins provides temporary protection to the newborn against antigens that the mother had been exposed to during her own life²⁴.

Because of the great importance of this process, we investigated in a clinical setting the placental transmission of IgG antibodies in term and preterm newborns.

In the present work we found that through the third trimester of gestation, total IgG levels in both mothers and neonates showed a significant increase towards the end of gestation.

Surprisingly in the mothers, both statistical tests applied indicated a mild, yet significant increase in IgG levels over the course of the last trimester. A large number of studies have been conducted on the relationship between IgG levels during pregnancy in the first, second and the third trimester, reporting a significant drop throughout gestation²⁶. This gradual decline in IgG was described as a consequence of the physiological expansion of maternal blood volume (hemodilution) and is consistent with a similar change in i.e. albumin levels²⁶. However, little is known about the subtle changes developed exclusively during the third trimester. To our knowledge only a few studies have investigated this relationship and they reported no significant variations in maternal IgG concentrations between weeks 28 and 42 of gestation²⁶, or during the last 8 weeks of pregnancy²⁷. One report in Brazilian mothers suggested that although not statistically significant, mothers of preterm babies had lower IgG levels as compared with term babies' mothers²⁴. The reason for the slightly higher IgG levels found in our study remains unclear, although we might speculate a higher incidence of (subclinical) infections. We should also note that the higher data variation in groups III and IV could factor in to the trend we observed (Table I).

Regarding the newborns, our results were consistent with the scarce literature available. As early as 1967, Hobbs et al.²⁸ found an exponential relationship between total IgG and gestational age in preterm infants. In their review, Van den Berg et al.²⁹ clearly demonstrated that in the first trimester, very little IgG is transported to the fetus. In the second trimester, the fetal IgG rises from approximately 10% of the maternal concentration at 17–22 weeks of gestation to 50% at 28–32 weeks of gestation. In the third trimester, the increase of fetal IgG concentration between 29 and 41 weeks of gestation is two times as high as between 17 and 28 weeks of gestation³⁰. Similarly, other authors asserts that the immune transfer begins slightly earlier at 16 weeks of gestation, and that between the 22nd and 26th week, the level of fetal IgG increases rapidly doubling the IgG concentration at the end of gestation³¹. The greatest rate of antibody transfer to the fetus is after 34 weeks of pregnancy⁵.

Also, in all four groups studied in our work, the newborn's IgG levels exceeded their mother's values by a ~2.4%. Several studies have described similar findings. As human pregnancy progresses, fetal/newborn IgG levels continuously increase to reach and even surpass maternal levels at the end of the third trimester, resulting in a fetal:maternal ratio higher than one and sometimes reaching more than twice the maternal concentrations at the time of delivery^{32,33,34,35}. Assuming that these levels of IgG in the fetus are entirely of maternal origin, this would remarkably suggest that FcRn is able to transport this macromolecule against a concentration gradient.

On the other hand, our results agree with those reported by Palmeira et al.²⁵, who found that maternal age and parity do not seem to influence placental antibody transfer.

In our study, IgG was observed to increase significantly with the newborns weight at birth; it is likely that this association is due to the fact that infants delivered at later gestational weeks usually present a higher body weight²⁷. However, some, but not all investigators also have noted reduced circulating IgG concentrations in low birth weight infants, compared to those of similar gestational age with normal birth weight³⁶. This suggests that for a given gestational age, placental insufficiency may limit IgG transfer to the fetus³⁷.

Finally, the present work also demonstrated that a higher expression of the placental neonatal receptor FcRn was detected in placentas obtained from newborns at week 36 of gestation onwards. This is consistent with previous observations that expression of the FcRn receptor is dependent on gestational age and is at its highest in the third trimester of human pregnancy^{38,25}. In this regard, it is known that in placental tissues these receptors are mainly located in the apical side and cytoplasm of the syncytiotrophoblast³⁹. At early stages of pregnancy, the inner cytotrophoblast forms a continuous layer between the syncytiotrophoblast and the stromal cells. Cytotrophoblast cells neither express FcRn⁹, nor contain IgG, and may prevent further penetration of the villi by IgG⁴⁰. However, late in this period the FcRn is already expressed⁹. As gestation progresses and after the fourth month of pregnancy, the cytotrophoblast layer slowly disappears from the walls of the tertiary villi and becomes discontinuous, when the chorionic villi surface increments and expands, therefore exposing the syncytiotrophoblast cells to maternal blood vessels⁴¹. It is in this stage of gestation when the receptor can be exposed and the active transport of IgG begins. Experimental data obtained in rats indicated that the increasing total IgG levels during gestation coincides with an increase in FcRn expression in the placental tissue throughout pregnancy⁴².

To summarize, our results obtained from clinical samples, were in line with previous descriptions in model systems and confirmed that the amount of IgG transfer from maternal serum to the fetus is positively correlated with FcRn expression in placental tissue throughout gestation. The elucidation and full understanding of the physiological processes involved in the placental transfer of IgG antibodies is crucial to establish therapeutic protocols to treat immunodeficient mothers, as well as to allow comprehensive clinical care and management of the preterm newborn.

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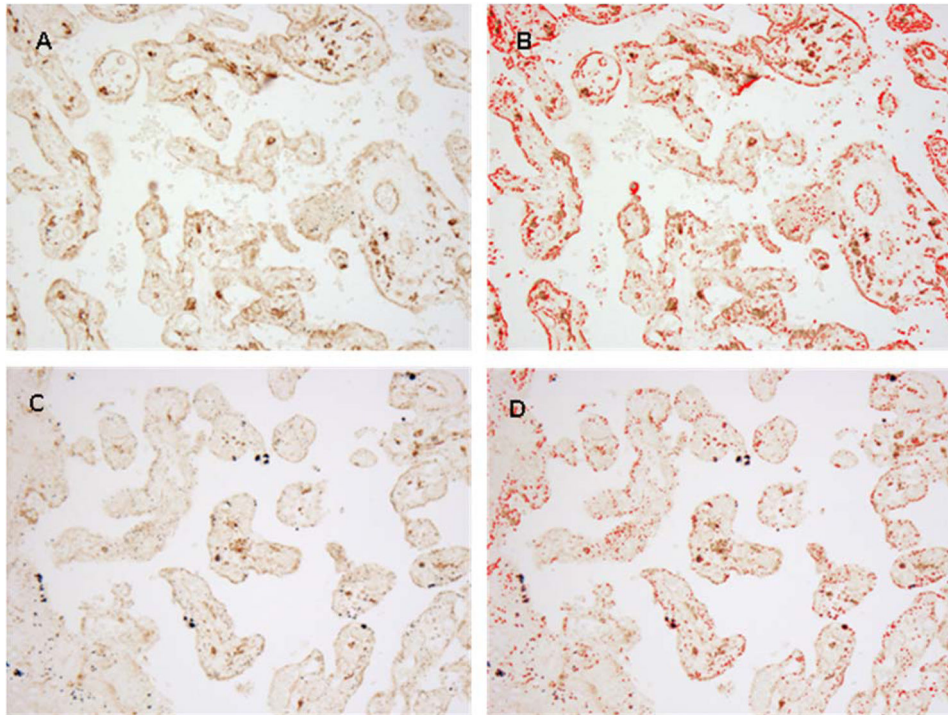


Figure 1. Representative figure of the FcRn expression in human placental tissue (20× magnification) in term and pre-term newborns before and after ImageJ processing (A vs. B and C vs. D, respectively).

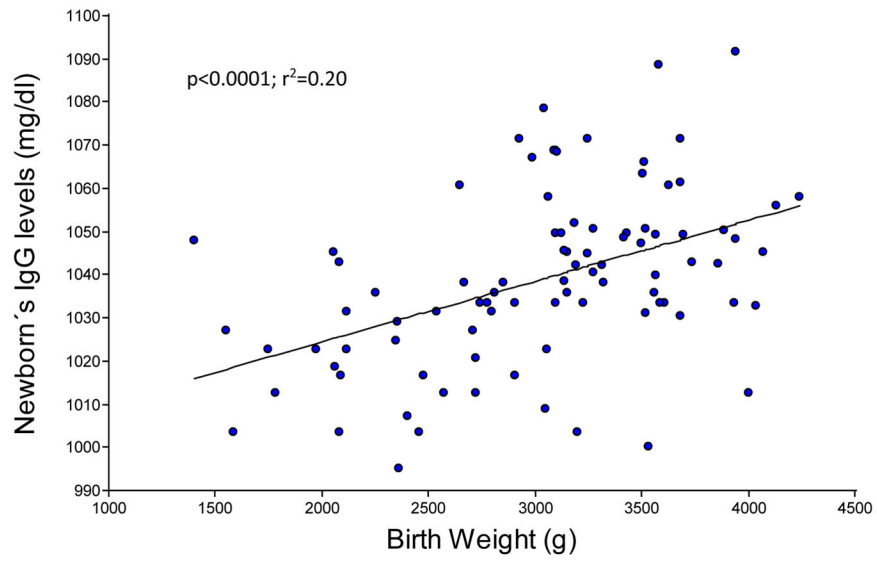


Figure 2. Newborn IgG levels and body weight increase during third trimester of gestation (n=90).

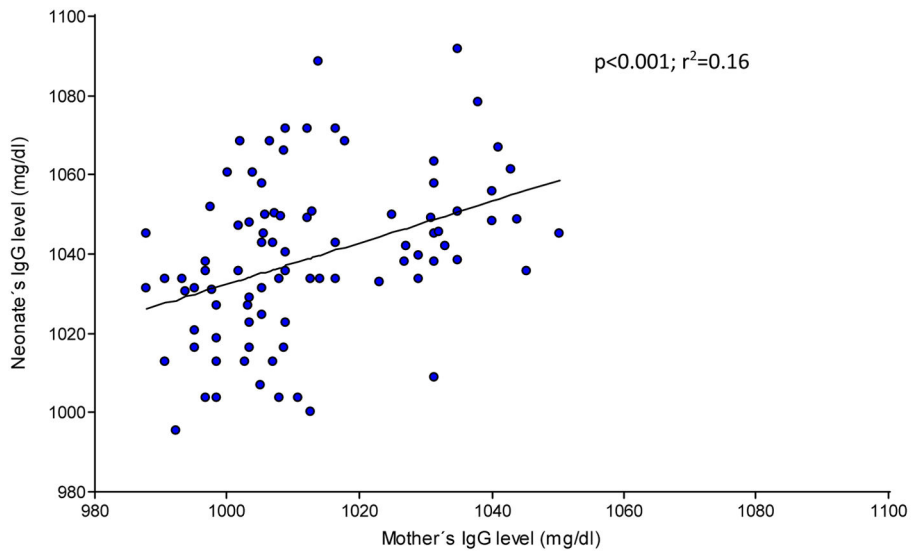


Figure 3. Relationship between mother's (n=85) and neonate's IgG levels (n=90).

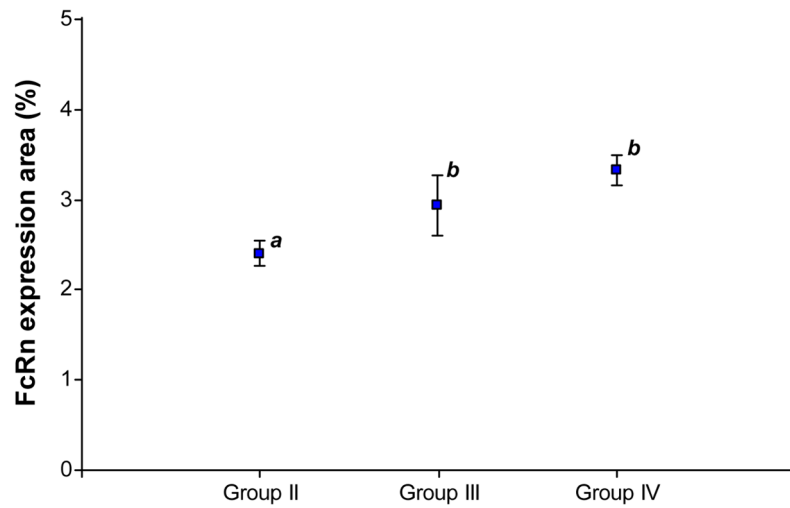


Figure 4. FcRn expression in human placental tissue during the third trimester of gestation. Group II: 34–35 weeks (n=7); Group III: 36–37 weeks (n=5); Group IV: 38–41 weeks (n=18). a vs b: p=0.004. Group I is excluded from the figure because it consists of a single sample of placental tissue.

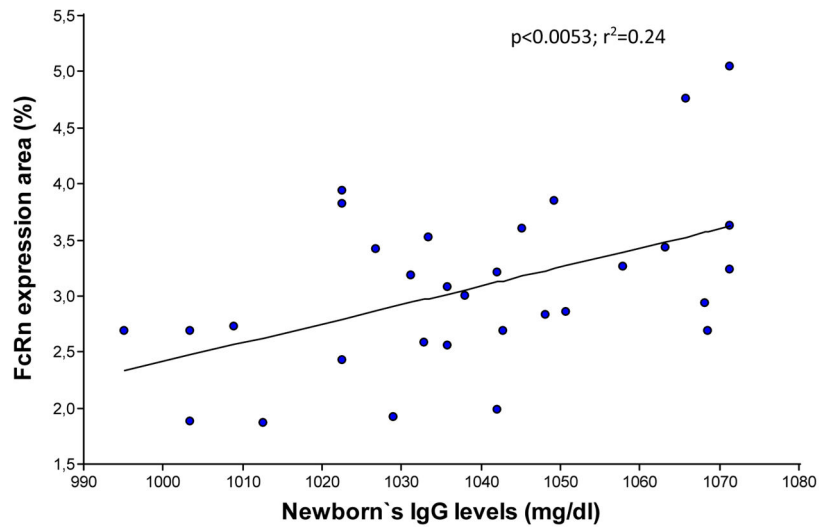


Figure 5. Relationship between percentage of the total area in the placental tissue with FcRn expression and the newborn's IgG levels (n=31).

Table 1

Clinical data and IgG levels in mothers and their newborns during the third trimester of gestation.

Mothers	Group I	Group II	Group III	Group IV
n	7 (8.2%)	12 (14.1%)	8 (9.4%)	58 (68.2%)
Age (years)	31 (26–37)	33 (31–37)	30 (30–32)	31 (29–34)
IgG levels (mg/dL)	998.4 (995.2–1003.5) ^a	1001.8 (992.2–1005.3) ^a	1003.5 (996.8–1007) ^a	1013.9 (1007.2–1031.3) ^b
Neonates	Group I	Group II	Group III	Group IV
n	8 (8.9%)	15 (16.7%)	9 (10%)	58 (64.4%)
Weight (g)	2032.5 (1585–2115)	2250 (2065–2460)	2800 (2725–3050)	3367.5 (3105–3680)
IgG level (mg/dL)	1014.55 (1007–1022.6) ^a	1029.1 (1003.5–1035.8) ^a	1022.6 (1016.5–1031.3) ^a	1046.35 (1035.8–1057.9) ^b

Values are expressed as median and range (Q1–Q3). Weeks of gestation: Group I: 32–33 weeks; Group II: 34–35 weeks; Group III: 36–37 weeks; Group IV: 38–41 weeks. a vs b: p<0.001.