Maternal allergen-specific IgG may protect the child against allergic sensitization – literature review

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Abstract

Introduction. *The analysis of allergen-specific IgE responses in birth cohorts with micro-arrayed allergens has provided detailed information regarding the evolution of specific IgE responses in children. Data regarding early development of allergen-specific IgG are needed.* ***Materials and method.*** *We analyzed the results obtained by searching for keywords "maternal allergens", "specific IgG", and "sensibilization" in PubMed and Elsevier databases. There were identified a number of 1984 publications, of which we kept exclusively those in extenso describing results of randomized studies. The studies were analyzed in order to identify the following variables: specific IgG dosage of maternal allergen in the third trimester, the identification of IgG in cord blood, and allergic reactions of children at two months, six months, one year and at five years.* ***Results and discussion.*** *A number of two studies have identified the fact that all children from mothers with elevated (>30 ISU) specific plasma IgG against an allergen did not have IgE sensitization against that allergen at the age of 5 years old.* ***Conclusions.*** *The latest studies in the field have shown that high levels of IgG specific to allergen in mothers during the third trimester and in cord blood seem to protect against allergic sensitization in children. This finding has clinical implications for the prevention of allergies, as well as in their treatment. Studies on human subjects are limited, but the experimental ones are promising, more studies being needed on this topic.*

Keywords: *allergen specific IgG, children allergic sensitization, allergy prevention*

Rezumat

Introducere. *Analiza răspunsurilor IgE specifice alergenului în cohortele de naștere cu alergeni micromatrice a furnizat informații detaliate privind evoluția răspunsurilor IgE-specifice la copii. Sunt necesare date privind dezvoltarea timpurie a IgG specifice alergenului.* ***Materiale și metodă.*** *Am analizat rezultatele obținute prin căutarea cuvintelor-cheie „alergeni materni", „IgG specific" și „sensibilizare" în bazele de date PubMed și Elsevier. A fost identificat un număr de 1984 de publicații, dintre care le-am reținut exclusiv pe cele in extenso care descriau rezultatele unor studii randomizate. Studiile au fost analizate în vederea identificării următoarelor variabile: dozările IgG specifice ale alergenului matern în trimestrul al III-lea, identificarea IgG în cordonul ombilical, reacțiile alergice ale copiilor la două luni, șase luni, un an și la cinci ani.* ***Rezultate și discuții.*** *Un număr de două studii au identificat faptul că toți copiii proveniți din mame cu valori crescute (>30 ISU) ale IgG plasmatice specifice împotriva unui alergen nu au avut sensibilizări IgE împotriva acelui alergen la vârsta de 5 ani.* ***Concluzii.*** *Ultimele studii în domeniu au demonstrat faptul că nivelurile ridicate de IgG specifice alergenului la mame în timpul trimestrului al III-lea și în sângele din cordonul ombilical par să protejeze împotriva sensibilizării alergice la copii. Această constatare are implicații clinice pentru prevenirea alergiilor, precum și în tratamentul acestora.*

Cuvinte-cheie: *alergen specific IgG, sensibilizarea alergică a copiilor, prevenirea alergiei*

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IgG alergen-specifice materne pot proteja copilul împotriva sensibilizării alergice. Review al literaturii

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Background

In the literature, there are studies that target the immune response of the newborn, cellular-mediated and hypersensitivity reactions, as well as the impact of the transfer of specific IgG antibodies to certain allergens from the mother to the fetus.

The hypothesis present in most specialty studies is that maternal sensitization to various allergens (the production of IgG against these allergens) induces, by transferring antibodies to the fetus, a tolerance and protection of the newborn. FcRn plays a key role in the immunity of the offspring, by mediating the transfer of maternal IgG in early life. Its functions are: protection from catabolism of IgG and albumin, bidirectional transport of IgG through the lumen and lamina propria, retrieval of IgG immune complex from the lumen and presenting it to the antigen-presenting complex macrophages and dendritic cells[(1)].

Materials and method

We analyzed the results obtained by searching for keywords "maternal allergens", "specific IgG" and "sensibilization" in PubMed and Elsevier databases. A number of 1984 publications were identified, of which we kept exclusively those *in extenso* describing results of randomized studies. The studies were analyzed in order to identify the following variables: specific IgG dosage of maternal allergen in the third trimester, the identification of IgG in cord blood, allergic reactions of children at two months, six months, one year and at five years. A series of rodent studies were also reviewed in order to specify the role of the experimental work in the field.

Results and discussion

The human placenta represents a histological barrier separating the maternal blood from that of the neonate and consists of two layers: the syncytiotrophoblast and the endothelial cells of the fetal capillaries. Molecules with low molecular weight (<500Da) will diffuse across the barrier, whilst those with high molecular weight will usually not. IgG is the only antibody transferred across the placenta in significant quantities, in spite of its molecular mass of 160 kDa. This process begins at about 13 weeks of gestation by binding with the neonatal FcRn. This receptor was first discovered in rats as the receptor that transfers the antibody from mother to offspring. IgG binds FcRn only at a pH lower than 6.5. FcRn is expressed in human intestinal macrophages, dendritic cells and monocytes from the peripheral blood[2,3].

Other maternal-fetal transfer mechanisms were discussed, the main being aspiration through amniotic fluid, and fetal skin permeation[4].

The method of transferring antibodies through breast milk was also discussed, as the FcRn receptors express themselves as well in the intestinal cells of the newborn. A paper published in 2010 highlighted that in laboratory animals, the deficit of the alpha chain or B2-microglobulin from the structure of the FcRn receptor leads to malabsorption of IgG antibodies in the intestinal level from breast milk[5]. The timing of maternal immunization appears to determine the intensity of the sensitivity reaction: the contact with allergens at the onset of pregnancy causes a strong reaction of sensitivity[6].

A large rodent study, published in 2018 by Ohsaki et al., demonstrated that sensitizing female mice before mating and during pregnancy protected the offspring from developing allergic responses to the same allergen. They epicutaneously sensitized female mice with ovalbumin (OVA) or saline at 6-8 weeks, over 9 days before mating and once weekly during pregnancy and breastfeeding. Then, the 6-8-week-old offsprings were also sensitized with OVA or saline followed by oral challenge at day 9. The results were remarkable: offsprings sensitized with OVA from unsensitized mothers (saline exposure) developed food allergic reactions (high production of IgE-specific OVA); after oral challenge, offspring showed systemic anaphylaxis. In contrast, OVA-sensitized offspring from sensitized mothers showed significantly decreased IgE production and systemic anaphylaxis[1] we epicutaneously sensitized female mice with ovalbumin (OVA. This study also presents the role of the IgG-IC transferred *via* breast milk. Mother mice sensitized with OVA were put to nurse and breastfeed offspring from unsensitized mother, along with sensitized offspring. The result was increased levels of serum OVA-IgG-IC in fostered offspring similar to those of sensitized offspring. These results indicate that breastfeeding by allergen-sensitized mothers offers protection from food allergy in offspring.

Various studies were aimed at determining IgG antibodies and IgG4 in maternal blood, umbilical cord blood and fetal blood[1,4,7]. The IgG profiles and levels appear to be similar in maternal and umbilical cord blood, thus emphasizing the maternal-fetal transfer of antibodies of this type. In a study conducted by N. Kamemura et al. in 2012 there were analyzed 92 pairs (mother-newborn) on the blood levels of IgG antibodies, IgG4, IgA, and IgE. In the case of mothers with allergies, for both food and inhalers, with positive IgG for various allergens, the presence of IgG antibodies in the umbilical cord blood has been highlighted in 91.2% of cases for food allergens and in 87.3% of cases for inhalator allergens[4].

This result demonstrates the transfer of IgG-type antibodies from mother to fetus. In previously immunized mothers, a new contact with the antigen during pregnancy acts by increasing the level of IgG antibodies, hence the transfer to the fetus, providing the protectiveness in the first months and even years of life[6].

Another study, on 99 families (mother-child), conducted recently by C. Lupinek et al., on 164 food allergens and inhalers, had the objective of highlighting the awareness-raising reaction by IgE in the newborn mothers presenting IgG against specific allergens. The ALADDIN cohort was used ("Assessment of Lifestyle and Allergic Disease During Infancy"). Samples of maternal blood were harvested in the third trimester of pregnancy, umbilical cord blood, breast milk at two months postpartum, and fetal plasma at 6, 12 and 60 months. IgG profiles were analyzed using micro-array techniques, and the analysis of IgE sensitization of the children at age 5 was conducted by allergen extract-based serology. It has been shown that when IgG levels in maternal blood were elevated (>30 ISU), there was no sensitization reaction to IgE in the fetal blood five years after birth[7].

Regarding allergen-specific immunotherapy, there are studies suggesting that the treatment of pregnant women can lead to the suppression of the development of IgE sensitization in the newborn, through the transplacental transfer of IgG[7]. A rodent study provides evidence that IC supplementation during pregnancy and breastfeeding further protect offsprings against food allergy. Maternal supplementation only during

breastfeeding period resulted in lower IgG-IC, thus showing the contribution of *in utero* IgG-IC transfer[1]. Current guidelines mention immunotherapy in pregnancy as an alternative.

Conclusions

The latest studies in the field have shown that high levels of IgG specific to allergen in mothers during the third trimester and in cord blood seem to protect against allergic sensitization in children. This finding has clinical implications for the prevention of allergies, as well as in their treatment. Some rodent studies provide experimental support of the potential beneficial effects of maternal allergen exposure during mating and pregnancy to protect offspring from food allergy and systemic anaphylaxis.

Studies on human subjects are limited, but the experimental ones are promising, more studies being needed on this topic. ■

Conflict of interests: The authors declare no conflict of interests.

References

1. Ohsaki A, Venturelli N, Buccigrosso TM, Osganian SK, Lee J, Blumberg RS, Oyioshi MK. Maternal IgG immune complexes induce food allergen-specific tolerance in offspring. *J Exp Med*. 2018 Jan 2; 215(1):91–113.
2. Sockolosky JT, Szoka FC. The neonatal Fc receptor, FcRn, as a target for drug delivery and therapy. *Adv Drug Deliv Rev*. 2015 Aug 30; 91:109–24.
3. Wilcox CR, Holder B, Jones CE. Factors affecting the FcRn-mediated transplacental transfer of antibodies and implications for vaccination in pregnancy. *Front Immunol*. 2017 Oct 13; 8:1294.
4. Kamemura N, Tada H, Shimojo N, Morita Y, Kohno Y, Ichioka T, et al. Intrauterine sensitization of allergen-specific IgE analyzed by a highly sensitive new allergen microarray. *J Allergy Clin Immunol*. 2012 Jul;130(1):113–121.e2.
5. Matson AP, Thrall RS, Rafti E, Lingenheld EG, Puddington L. IgG transmitted from allergic mothers decreases allergic sensitization in breastfed offspring. *Clin Mol Allergy*. 2010;8:9.
6. Fusaro AE, Brito CA, Victor JR, Rigato PO, Goldoni AL, Duarte AJS, Sato MN. Maternal-fetal interaction: preconception immunization in mice prevents neonatal sensitization induced by allergen exposure during pregnancy and breastfeeding. *Immunology*. 2007; 122(1):107–15.
7. Lupinek C, Hochwallner H, Johansson C, Mie A, Rigler E, Scheynius A, Alm J, Valenta R. Maternal allergen-specific IgG may protect the child against allergic sensitization. *J Allergy Clin Immunol*. 2019; pii: S0091-6749(19)30106-X.