

Correspondence and Replies

RE: Cesarean section implicated in more long-term medical problems

TO THE EDITOR:

We read with interest the letter by Radano et al¹ regarding the association between birth by cesarean section (CS) and early antibiotic use and eosinophilic esophagitis. More and more data support that, in many children, the effects of dysbiosis may be long lasting. We had reviewed the records of 12 patients with eosinophilic gastrointestinal disorders seen for 11.6 years.² All 5 children born by CS required corticosteroids for remission and long-term management, and only 1 is presently in remission. Only 2 of 7 delivered vaginally (VD) required corticosteroids, and 5 remain in remission and tolerate a polymeric diet, although 2 still require a hypoallergenic diet but not corticosteroids. The median eosinophil count in CS was 1464 versus 484 cells/ μ L in VD ($P = .07$, calculated by the Mann-Whitney test). Four of 5 babies born by CS had an eosinophil count >600 cells/ μ L, whereas only 3 of 7 of VD. This limited observation would indicate that CS may be associated with the degree of severity of eosinophilic gastrointestinal disorders, and, although patients with eosinophilic gastrointestinal disorders have different areas of the bowel affected than those with eosinophilic esophagitis, our findings support those described by Radano et al.¹

CS has been associated with increased levels of IL-13 and IFN- γ in newborns, perhaps because of the lack of labor and/or reduced exposure to specific microbes at birth.³ The mode of delivery also influences the bacterial diversity of breast milk. Milk samples from mothers who had undergone elective but not emergency CS had decreased amounts of Leuconostocaceae and increased amounts of Carnobacteriaceae, among others, compared with those who were born via VD, which suggests that it is not the operation *per se* but rather the absence of physiological stress or hormonal signals that could contribute to an aberrant microbial transmission process to breast milk.⁴ When considering that Radano et al¹ series is relatively large, it would be interesting if they could determine what proportion of their patients were born by elective CS versus emergency.

Carlos Lifschitz, MD^a

Veronica Busoni, MD^a

Marina Orsi, MD^a

Silvia Christiansen, MD^b

Maria Teresa Davila, MD^c

^aSection of Pediatric Gastroenterology, Hepatology and Transplantation, Hospital Italiano, Buenos Aires, Argentina

^bDepartment of Pathology, Hospital Italiano, Buenos Aires, Argentina

^cDepartment of Pathology, Children's Hospital "JP. Garrahan," Buenos Aires, Argentina

No funding was received for this work.

Conflicts of interest: C. H. Lifschitz is on the Nestlé Nutrition Institute Advisory Board; has received consultancy fees from Sequoia z.o.o.; has received lecture fees from Nestlé Nutrition Institute, Mead Johnson Nutrition, IPSEN; and has stock/stock options in Mead Johnson Nutrition. V. Busoni has received travel support from Nutricia; has received lecture fees and fees for participation in review activities from SHS; has received research support from Roemmers; and has received travel support from Nutricia, Merck, and Mead Johnson. M. Orsi and

S. Christiansen have received lecture fees and travel support from Mead Johnson, Nestlé, and Nutricia. M. T. Davila declares that she has no relevant conflicts of interest.

Received for publication May 23, 2014; accepted for publication June 17, 2014.

Corresponding author: Carlos Lifschitz, MD, Section of Pediatric Gastroenterology, Hepatology and Transplantation, Hospital Italiano, Juan D. Peron 4190, Buenos Aires, Argentina C1171ACH. E-mail: carlos.lifschitz@hospitalitaliano.org.ar.

2213-2198

© 2014 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2014.06.013>

REFERENCES

1. Radano MC, Katz A, Kubala S, Keet CA, Yuan Q, Fleming JT, et al. Cesarean section and antibiotic use found to be associated with eosinophilic esophagitis. *J Allergy Clin Immunol Pract* 2014;2:475-7.
2. Busoni V, Orsi M, Christiansen S, Davila MT, Lifschitz C. Is delivery by cesarean section a risk factor for persistence and severity in eosinophilic gastroenteropathy in pediatric patients? *J Pediatr Gastroenterol Nutr* 2012;54:829.
3. Ly NP, Ruiz-Pérez B, Onderdonk AB, Tzianabos AO, Litonjua AA, Liang C, et al. Mode of delivery and cord blood cytokines: a birth cohort study. *Clin Mol Allergy* 2006;4:13.
4. Cabrera-Rubio R, Collado MC, Laitinen K, Salminen S, Isolauri E, Mira A. The human milk microbiome changes over lactation and is shaped by maternal weight and mode of delivery. *Am J Clin Nutr* 2012;96:544-51.

REPLY:

We thank Lifschitz et al¹ for their comments on our recent article.² In our article, we found that children with eosinophilic esophagitis were more likely to have been born by cesarean section than healthy controls. Lifschitz et al¹ suggest that this increased risk and that found in other allergic and gastrointestinal diseases, might be explained by the downstream effects of the lack of exposure to labor and its associated physiological stresses and hormonal signals in children born by planned cesarean section rather than differences in exposure to the vaginal microbiota. The idea that exposure to labor may be as important as exposure to the vaginal microbiome is an intriguing one, as is the suggestion that altered breast milk microbiota may play a role. However, because many nonelective cesarean deliveries occur after rupture of membranes, separating exposure to vaginal flora from experience of labor may not be simple.

Moreover, there now is a body of literature that shows that children born by cesarean section have altered development of the gut microbiome³ and demonstrate the importance of microbial exposure in the developing immune system.⁴ Dysbiosis as a mechanism for accounting for the association between the mode of delivery and allergic disease also is attractive to us because of its potential explanatory power for the association of eosinophilic esophagitis with both the cesarean mode of delivery and the antibiotic use in the first year. In our study, unfortunately, we do not have data on an indication for cesarean delivery and so cannot comment on whether it is cesarean delivery *per se* or lack of labor that increases the risk of eosinophilic esophagitis. We concur that future research on the mode of delivery and allergic disease should include analysis of associations with the type of cesarean delivery.

Lifschitz et al¹ also hypothesize that cesarean delivery might be associated with increased severity of eosinophilic gastrointestinal diseases. Our study was not designed to look at severity of eosinophilic esophagitis, and so we cannot comment on whether severity of eosinophilic esophagitis is associated with mode of

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.