



## Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica,  
Alergología y Asma Pediátrica

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### EDITORIAL

## Factors that increase wheezing risk in nursing infants in the first year of life



Wheezing, and especially recurrent wheezing, is an important problem during the first years of life. Its increasing prevalence, the lack of specificity of the clinical manifestations, its association to viral infections and to the ulterior development of asthma, and the variability of patient response to treatment, define wheezing as a complex disorder that constitutes a major health problem and affects the quality of life of the affected children and their families.<sup>1</sup> The development of tools for the early detection of infants at increased risk of suffering wheezing is essential in order to establish a prognosis and prescribe treatments which, while not able to heal the disorder, may reduce morbidity and improve patient quality of life during the first few years after birth.<sup>2</sup>

Epigenetic factors play a key role in the development of asthma and other allergic processes.<sup>3</sup> Since the genetic profile of humans has changed little over the last few thousands of years, the mechanisms underlying the increase in prevalence of these diseases observed over the last few decades must be attributed to different environmental factors.<sup>4</sup> In this regard, in-depth knowledge of such factors may offer physicians and parents the opportunity to modify those circumstances that contribute to the appearance of recurrent wheezing and the development of asthma in nursing infants and pre-school children.

A group of Spanish investigators participating in the International Study of Asthma and Allergies in Childhood (ISAAC) has developed the International Study on Wheezing in Infants (*Estudio Internacional de Sibilancias en Lactantes* [EISL]).<sup>5</sup> The EISL is a cross-sectional, multicenter observational study with the main purpose of determining the prevalence, frequency and severity of wheezing in different centers in Europe and Latin America, and of defining the risk factors that favor the appearance of wheezing problems in the first year of life.

The present number of *Allergologia et Immunopathologia* includes three epidemiological studies based on the methodology of the EISL and which aim to improve our knowledge of the factors that increase the risk of

wheezing, asthma, rhinitis and atopic dermatitis during the first years of life.

The first of these studies involved 1065 nursing infants in Pamplona, and made use of a standardized questionnaire.<sup>6</sup> The prevalence of wheezing and of recurrent wheezing at 12 months of age was 31.2% and 12.3%, respectively, and the presence of respiratory infections and eczema was seen to be associated to an increased risk of wheezing. It is important to note that the analysis of the results was based on the Chi-squared test, which is unable to establish the directionality of the associations (i.e., whether a given finding is a cause or consequence). In other words, it cannot be used to determine whether children susceptible to wheezing are at increased risk of developing infections and eczema, or the other way around. Another risk factor identified in this study refers to passive tobacco smoke exposure among nursing infants. In this case causal directionality could be established, since exposure to tobacco smoke during pregnancy has been correlated to worsened lung function – thus pointing to an important influence in development of the disease. In the same way as in other studies, the authors found that a history of asthma, rhinitis and dermatitis in the parents increased the risk of wheezing in the offspring – thus suggesting an important hereditary component in the development of asthma and other allergic processes, especially when both parents are affected.

The second study was carried out in Salamanca with the aim of identifying factors that increase the risk of wheezing in 1164 nursing infants, and of defining measures against such factors.<sup>7</sup> A validated questionnaire was used for this purpose, with questions referred to pregnancy and the first year of life of the infant. The prevalence of wheezing at 12 months of age was 32.3%. The multivariate analysis concluded that infants with eczema, that attend nursery school and with mothers that have asthma, smoked during the last three months of pregnancy, and did not consume a Mediterranean diet during pregnancy, were at a very high risk of suffering recurrent wheezing during the first year of life. An interesting aspect of this study is that it allowed the

development of a predictive model involving the application of algorithms based on the presence or absence of asthma in the mother – combining the rest of risk factors to obtain an individualized estimate of the probability of suffering recurrent wheezing at 12 months of age. In this respect, when the infants presented the abovementioned risk factors, the probability of developing wheezing was found to be 79.7%. In contrast, the estimated risk was only 4.1% among those infants that presented none of the mentioned factors. Ideally, this predictive model should be applied from the neonatal period, with a view to adopting adequate preventive actions. Furthermore, in order to increase the reliability of the model, it should be developed on a local basis, since there may be variations in risk factors conditioned to the geographical setting and to aspects referred to local life style, among other parameters.

The third study was carried out in Cartagena in 1000 pre-school children with the aim of assessing the effect of certain foods and the Mediterranean diet during pregnancy and the first years of life upon the development of wheezing, rhinitis and dermatitis.<sup>8</sup> One of the employed questionnaires evaluated infants at 15 or 18 months of age, analyzing the maternal diet during pregnancy. Another questionnaire in turn evaluated the infants at four years of age. The prevalence of wheezing, rhinitis and dermatitis at this age was 18.8%, 10.4% and 17.2%, respectively. The results of the study suggested that a low maternal intake of fruit and a high intake of meat, pasta and potatoes during pregnancy constitute risk factors for wheezing, rhinitis and dermatitis. On the other hand, the consumption of fast food on the part of both the infants and mothers failed to yield clear results. The authors concluded that the Mediterranean diet does not offer protection against the mentioned disease conditions, in contrast to the conclusions of a metaanalysis involving almost 40,000 children.<sup>9</sup>

The Mediterranean diet was declared an immaterial cultural heritage of mankind by the UNESCO in November 2010. It is claimed to offer healthy effects, and includes the frequent consumption of fruit, vegetables, nuts, cereals, olive oil and fish. Although the results are controversial, the consumption of antioxidants (fruit, vegetables and fish) has been related to a lesser prevalence of asthma and other allergic diseases. In contrast, a diet rich in saturated fats has been associated to an increased risk of such disorders. Paradoxically, a large part of the Mediterranean population is abandoning this type of diet in favor of fast food and/or pre-cooked foods, saturated fats and meat. This situation, together with an increasingly sedentary lifestyle, appear to be among the leading causes of the observed increase in the prevalence of obesity and other associated diseases such as asthma, in this geographical setting.

Although the data from the studies suggest the existence of an association between diet and the initiation and development of asthma, no clear scientific evidence has yet been obtained to allow the recommendation of concrete primary prevention measures in either the general population or in the different patient sub-types. Although the nutritional hypotheses are promising, and despite the existence of partial findings associating diet to the development of asthma or allergy, there is no evidence that any given food or type of diet is able to exert a preventive effect against asthma after the first few years of life. If any such effect exists, it is

probably restricted to a concrete “window of opportunity” during the prenatal period and first months of life – a critical phase in which it may still be possible to modulate the development and growth of organs such as the skin and respiratory apparatus, and the digestive and immune systems. Such interactions in turn would have repercussions for the rest of the life of the individual. Hence the importance of identifying epidemiological, clinical and biochemical markers capable of establishing an early prediction (ideally during pregnancy) of the risk of developing diseases of this kind – with a view to adopting early preventive measures.

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