

Short Communication

Fetal growth promotion in allergic children

Kawano Y, Morikawa M, Watanabe M, Ohshiba A, Noma T, Odajima H. Fetal growth promotion in allergic children.

Pediatr Allergy Immunol 2005; 16: 354–356. © 2005 Blackwell Munksgaard

Several *in vitro* studies have suggested the presence of Th2-skewed immunity during pregnancy in infants with atopic diseases. Our study indicated that allergic infants showed a higher birth weight and shorter gestational period at birth than those of non-allergic peers. Moreover, allergic mothers gave birth to neonates whose birth weights and gestational ages were higher and shorter than those of the non-allergic mothers, respectively. Thus, our data clearly demonstrated the promotion of intrauterine growth, either in the allergic children, or allergic mothers. Such an intrauterine environment favorable for the fetal growth may also accelerate the development of allergic diseases in their offspring that are most probably caused by the Th2-oriented immunity.

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Key words: fetal growth; birth weight; gestational age; development of allergy; atopic dermatitis; bronchial asthma; Th2

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Accepted 14 March 2005

Successful pregnancy requires a maternal immunity biased toward Th2 rather than Th1 (1). Several *in vitro* studies have presented evidence of a Th2-skewed immune response in the atopic children, coming as early as the moment of birth itself (2). A delayed maturation of the Th1 response may lead to the development of the allergic diseases in the infants during the first 2 yr of life (3). However, clinical data that support such an increased bias toward Th2 in the potentially allergic newborns is still lacking.

About 279 children of 1 yr old, including 142 males and 137 females, who visited the pediatric clinics at one of our hospitals in Japan asking for requesting medical care or for a health examination were enrolled into this study. Any controls, who, are attending due to any condition that is linked to low birth weight were excluded. Data on birth weight and gestational age was obtained from the medical record. The mothers of the children, that were eligible for the detailed questionnaire modified from that provided by the International Study of Asthma and Allergies

in Childhood (ISAAC) (4) were asked about the birth conditions reflecting the intrauterine period of life. Informed consent was also obtained from the mothers.

Based on the questionnaire and physical examinations, the presence or absence of maternal allergic diseases was determined. Allergic mothers were defined as having at least one of the five major allergic diseases, including bronchial asthma, atopic dermatitis, allergic rhinitis, Japanese pollinosis and allergic conjunctivitis, whereas mothers having with none of the above these five allergic disorders were diagnosed as non-allergics.

The diagnosis of atopic dermatitis was based on a physical examination by pediatric allergologists according to the Hannifin and Rajka criteria (5). Typical morphology and distribution such as facial and extensor involvement and chronic or chronically relapsing dermatitis were two important criteria. The other two factors including onset at an early age and a personal or family history of atopy were omitted, because

they were not useful for young children in this study. Similarly, children having experienced recurrent wheezing episodes confirmed by medical records were diagnosed as having asthmatic by pediatric allergologists, based on the criteria of the American Thoracic Society (6). Of the 279 children in the present study, 50 (18.0%) had atopic dermatitis and 52 (18.6%) had bronchial asthma. About 20 (7.2%) had both of them. Mann–Whitney *U*-test was used to analyze the data.

As shown in Table 1, the birth weights of the allergic children, having either atopic dermatitis or bronchial asthma, were significantly higher than those of non-allergics and the gestational period at birth of the allergic children was also significantly shorter than those that of non-allergics (Mann–Whitney *U*-test; $p < 0.001$). Similarly, children with atopic dermatitis showed higher birth weights and shorter gestational ages than those without this condition, while the presence or absence of bronchial asthma also revealed the same trends (Mann–Whitney *U*-test; $p < 0.001$).

In addition to the presence or absence of the infantile allergic diseases, the allergic status of their mothers may affect the development of allergy in their offspring. Thus, allergic mothers gave birth to neonates whose birth weights and gestational ages were higher and shorter than those of the non-allergic mothers, respectively, as in Table 2 (Mann–Whitney *U*-test; $p < 0.001$).

To confirm the data of Mann–Whitney *U*-tests, logistic regression analysis was constructed by using birth weight, gestational age, infantile gender, maternal infection during pregnancy and respiratory infections early in infancy. The results of the logistic regression analysis indicated that birth weight increased the risk of allergy and atopic dermatitis, but not that of bronchial asthma.

Previous studies have indicated an association between the development of atopic diseases and the birth weight and the gestational age (7–10).

Table 1. Comparisons of the weights and gestational periods at birth between allergic and non-allergic children

Status of the children	Birth weight (g)	Gestational period (wk)
Allergy (+)	3040.4 $\pm$ 441 (n = 82)*	38.76 $\pm$ 1.71 (n = 68)*
Allergy (–)	2891.5 $\pm$ 418 (n = 190)	39.48 $\pm$ 7.10 (n = 157)
Atopic dermatitis (+)	3095.2 $\pm$ 389 (n = 50)*	39.17 $\pm$ 1.41 (n = 42)*
Atopic dermatitis (–)	2900.6 $\pm$ 431 (n = 222)	39.29 $\pm$ 6.63 (n = 183)
Bronchial asthma (+)	3012.5 $\pm$ 455 (n = 52)*	38.47 $\pm$ 1.97 (n = 43)*
Bronchial asthma (–)	2918.4 $\pm$ 422 (n = 220)	39.46 $\pm$ 6.60 (n = 182)

Data represent mean $\pm$ s.d.

*Mann–Whitney *U*-test $p < 0.001$.

Table 2. Comparisons of the weights and gestational periods at birth between neonates born to allergic and non-allergic mothers

Status of the mother	Birth weight (g)	Gestational period (wk)
Allergy (+)	2949.64 $\pm$ 353.143 (n = 98)*	38.7326 $\pm$ 3.4791 (n = 86)*
Allergy (–)	2928.97 $\pm$ 468.102 (n = 174)	39.3857 $\pm$ 7.53179 (n = 140)

Data represent mean $\pm$ s.d.

*Mann–Whitney *U*-test $p < 0.001$.

However, our data did not correlate with the study by Olesen et al., who demonstrated that a high birth weight and high gestational age were associated with an increased risk of atopic dermatitis (7). Moreover, another alternative research indicated that the risk for adult asthma is partly established early in life and suggests that poor intrauterine growth is involved in the etiology of asthma (8). The reasons for the discrepancy between their results and ours might be result from the difference in the age of the subjects involved.

In contrast, the results shown here are consistent with the data of the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study (10), that indicated a high birth weight increase was associated with a risk of atopic dermatitis in the first year of life for infants born to mothers with a respiratory allergy and with the study by Yuan et al. (9) showing that fetal growth was associated with childhood asthma. Unlike those researches, our subjects included not only allergic mothers, but also healthy mothers and our study analyzed two representative allergic diseases: namely atopic dermatitis and bronchial asthma. Moreover, the other study focused on the birth weight and gestational age outside the normal range and they concluded that babies outside normal birth weight or gestational ages, seemingly the result of abnormal pregnancies, were at risk of allergy. However, our study targeted infants born with a normal range of their birth weight and of their gestational age, which suggests that some factors promote the development of childhood allergy during a normal pregnancy. The difference in birth weights and the gestational ages between allergics and non-allergics in the present research was small and within the normal range, but it includes statistically significant differences such as $p < 0.001$.

Although factors other than birth weight and gestational age may affect the development of allergy in their children, the gender of the infant, maternal age, use of antibiotics, breast feeding, environmental smoking, pet exposure or daycare attendance were not found to be associated with

allergy. Infantile respiratory infection during infancy was associated with the development of bronchial asthma, in contrast to maternal infections during pregnancy that did not affect any allergic diseases (data not shown).

Since the atopic dermatitis and bronchial asthma conditions were independently associated with increased fetal growth promotion, it is highly likely that the development of allergic disease and a fetomaternal interface favoring fetal growth are closely linked, although our data must be regarded as preliminary given the size of the study. Nevertheless, these results strongly suggest that the exceedingly Th2-oriented fetoplacental environment present in allergic individuals also promotes fetal growth.

Acknowledgments

This study was partly supported by Research on Allergic Diseases and Immunology of Health and Labour Sciences Research Grants in Japan.

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