

Exposure to peanuts *in utero* and in infancy and the development of sensitization to peanut allergens in young children

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This study attempted to determine the underlying factors that may influence the development of peanut sensitization in young children in South Africa. One of our objectives was to ascertain whether the consumption of peanuts or peanut-containing foods during pregnancy and lactation by mothers from atopic families impacted upon the development of an allergic response to peanuts in the child. Forty-three children between the ages of 0 and 3 yr participated in this study. There were 25 peanut-sensitized subjects and 18 control subjects (children sensitized to milk and/or egg, but not to peanuts). A significant association was found between peanut sensitization and sensitivity to soya ($p=0.0002$), wheat ($p=0.03$), and cod fish. We found that mothers who consumed peanuts more than once a week during pregnancy were more likely to have a peanut-allergic child than mothers who consumed peanuts less than once a week (odds ratio=3.97, 98% confidence interval 0.73–24). Peanuts or peanut butter was introduced into the child's diet from a significantly younger age in the peanut-allergic subjects ($p<0.03$). There was a positive correlation in the peanut-allergic subjects between age of introduction of peanuts and age at the onset of symptoms ($r = 0.63$). Exclusive breast feeding did not protect against the development of peanut sensitization. Peanut allergy is associated with an increased risk of sensitization to other foods. It is more likely to occur if mothers eat peanuts more frequently during pregnancy and introduce it early to the infant's diet. These features highlight potentially avoidable factors that might prevent sensitization.

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The prevalence of peanut allergy appears to be increasing. This phenomenon parallels a general increase in the prevalence of atopic diseases worldwide; however, in communities where peanut consumption is traditionally high, such as in the United States, peanut sensitization is one of the leading causes of morbidity as a result of food allergy and is probably the leading cause of fatal or near-fatal reactions induced by foods (1). An increased exposure to peanut allergens in early life, via breast milk or *in utero* (2), may account for the onset of peanut allergies at an earlier age, in children younger than 2 yr (1, 3–5).

For non-allergic individuals, peanuts constitute a healthy, cheap, nutritious source of protein and energy and are a commonly eaten food for young children and adults in South Africa. An increased consumption of peanuts and peanut butter as foods or snacks has also been observed in the United States and in Europe (1–3). Mothers also seem to be eating more peanuts during pregnancy and/or lactation in recent years (2).

Controversy still surrounds the hypothesis that peanut proteins can sensitize the fetus via the placenta, or the breast-fed baby via the breast

milk, in mothers who consume peanuts during pregnancy and lactation (2, 4). Most of the studies on food avoidance suggest that there is an association between the prevalence of food allergy in infants and the consumption of 'allergenic' foods by pregnant or breast-feeding mothers (5–11). However, there is still some debate as to whether avoidance of certain foods in pregnancy can prevent or merely postpone the onset of allergies in infants and young children (9, 10).

It has been suggested that prior to overt exposure to peanut-containing foods as part of the regular diet, some infants may have been sensitized to peanuts by infant milk formulas that contain peanut protein or peanut (1–4, 12, 13). Peanuts and peanut products may be encountered as garnishes or ingredients in almost any meal and traces of peanut protein may contaminate the utensils previously used to prepare foods containing peanuts (1, 14). Peanut oils may also contain traces of allergenic proteins that could contaminate milk formulas and vitamin preparations (12, 13, 15–18).

Because peanut allergy belongs to the group of 'permanent' food allergies (1, 2, 5, 18), and is the most common cause of fatal and almost-fatal food-induced anaphylaxis (1, 3, 19, 20), early aggressive intervention in both prevention and treatment of peanut allergy is essential (1, 6–11).

This study has attempted to evaluate whether early and repeated exposure to peanut allergens during pregnancy and lactation is indeed a risk factor in the development of peanut sensitization.

Subjects and methods

The study design was a case-control, descriptive study.

Subjects

Children referred from the Red Cross Memorial Children's Hospital with suspected food allergy, aged between 0 and 3 yr at the time of diagnosis, were selected on the basis of radio-allergo-sorbent test (RAST) results. Tests to identify peanut, milk and/or egg sensitivity were performed at the Allergology Laboratory, University of Cape Town, using the Pharmacia CAP-RAST system (Pharmacia, Uppsala, Sweden). Levels of specific immunoglobulin E (IgE) greater than 0.35 kU/l were considered as positive for sensitization. An association between the positive RAST results and clinical symptoms was not confirmed by food challenge tests. Each child had a general clinical evaluation at the

Allergy Clinic, Red Cross Memorial Children's Hospital.

A standardized questionnaire was utilized to ascertain the nutritional intake and environmental and family history factors that may have contributed to the development of food allergy. The questionnaire, completed by the mother of each subject, sought information regarding maternal diet during pregnancy and lactation, as well as the child's feeding regimen from birth until presentation. Specific attention was paid to the consumption of peanuts and peanut-containing foods. The approximate age of onset of allergic symptoms in the child was also recorded. An attempt was made to minimize any informer bias by enquiring of the mothers about the intake of a wide variety of foods during pregnancy and lactation and by not revealing that the analysis of the study was focussed on peanut allergy.

On the basis of the RAST results, for the purpose of comparison, the subjects were divided into two groups: the peanut-sensitized children; and the control group (milk and/or egg-sensitive children).

The statistical programme epi info, Version 6, was used to analyze the results. p-values were considered to be significant if values were less than or equal to 0.05; 95% confidence intervals (CI) were used in the analysis of results. In view of the small numbers of children studied, Fisher's exact test was used to calculate a two-tailed p-value.

Ethics approval

The study was approved by the Research and Ethics Committee of the Faculty of Medicine of the University of Cape Town. Permission to conduct the study at Red Cross Children's Hospital was also granted.

Results

A total of 43 subjects between the age of 0 and 3 yr (26 males and 17 females) participated in this study. These subjects comprised 25 peanut-sensitized children and a control group of 18 milk and/or egg-sensitized children. There were no significant differences between the mean age, weight and height of the children in the two groups. The distribution of positive RAST to egg, milk, soya, wheat, and fish in the two groups is shown in Table 1. There was a significant positive association between peanut and soya sensitivity.

There were no significant differences between the peanut-sensitized and the control group with respect to allergic disease in the mother ($p=0.77$),

Table 1. Association of peanut sensitization with sensitization to other food allergens

Prevalence of other food allergies	Peanut-sensitized group	Control group	p-values
Egg	64%	88.9%	0.08
Milk	64%	61.1%	0.85
Soya	52%	0.0%	0.0002
Wheat	28%	0.0%	0.03
Fish (cod)	24%	0.0%	0.03

the grandparents ($p=0.18$) or the index child's siblings ($p=0.27$).

Peanut consumption by mothers during pregnancy

Table 2 depicts the relationship between the two groups regarding the consumption of peanuts by the mothers during pregnancy. Four mothers, two from the peanut-sensitized group and two from the control group, were uncertain about their consumption of peanuts during pregnancy and were therefore excluded from the analysis.

The odds ratio (OR) of 3.97 (95% CI 0.73–24) suggested that mothers who consumed peanuts more than once a week during pregnancy were almost four times as likely to have a peanut-allergic child than those mothers who consumed peanuts less than once a week during pregnancy. Although the p -value was not statistically significant ($p=0.063$), it suggests a strong trend that may be important for the prevention of sensitization to peanuts. Our results were, however, limited by the size of the patient sample.

Peanut consumption by mothers during lactation

Table 3 depicts the relationship between the two groups regarding the consumption of peanuts by the mothers during lactation. Two mothers from the peanut-sensitized group were uncertain about their consumption of peanuts during lactation and were therefore excluded from the analysis. No significant relationship was found between the two groups regarding peanut consumption by the mothers during lactation ($p=0.47$, OR = 2.19, 95% CI 0.39–13.47).

Table 2. Peanut consumption by mothers during pregnancy

Frequency of peanut consumption	Peanut-sensitized group (n=23)	Control group (n=16)
More than once weekly	11	3
Less than once weekly	12	13

$p=0.063$; odds ratio (OR)=3.97; 95% confidence interval (CI)=0.73–24.

The mean age of children at the introduction of formula in the peanut-sensitized group was 5.5 months and in the control group was 2.0 months. This suggests that exclusive breast feeding does not protect against the development of peanut sensitization.

Introduction of peanuts or peanut butter into the child's diet

The mean age and standard deviation for the introduction of peanuts or peanut butter into the child's diet into the peanut-sensitized group was 12.5 ± 6.4 months and in the control group was 17.3 ± 5.5 months ($p=0.03$). Nine subjects from the peanut-sensitized group and two from the control group had not yet, according to their mothers, consumed peanuts or peanut butter in their diet.

A positive correlation (Fig. 1) between the age of introduction of peanuts or peanut butter into the child's diet and the age of onset of symptoms (age of clinical diagnosis), was found in the peanut-sensitized group ($r = 0.63$; $p<0.05$).

There was no significant correlation in the control group between the age at onset of symptoms and the age of introduction of peanuts into the diet ($r = 0.14$).

Symptoms

Figure 2 shows the main symptoms that were evident on clinical examination of the subjects. Eczema, allergic rhinitis, seborrhoeic dermatitis, and diarrhoea were more prevalent in the peanut-sensitized group than in the control group. The prevalence of asthma was similar between the two groups. Eczema was the dominant symptom in the peanut-sensitized group and was prevalent in 88% of the subjects in this group. An OR of 7.0 suggested that the subjects in the peanut-sensitized group had a seven-fold greater risk of developing eczema compared with those in the control group. This was highly significant ($p=0.006$). The next most prevalent symptom in the peanut-sensitized group was asthma, followed by rhinitis and seborrhoeic dermatitis. However, the frequencies of these symptoms were not significantly different from the control group.

Discussion

Our study supports the hypothesis that early exposure to peanut allergens is a risk factor for the development of peanut sensitization (2, 3). We found that peanut consumption during pregnancy by the mothers of children in the peanut-sensitized group was greater than peanut con-

Table 3. Peanut consumption by lactating mothers

Frequency of peanut consumption	Peanut-sensitized group (n=23)	Control group (n=18)
More than once weekly	7	3
Less than once weekly	16	15

$p=0.47$; Odds ratio (OR)=2.19; 95% confidence interval (CI)=0.39–13.47.

sumption by the mothers of children in the control group. Although this is a small study, our data suggest that frequent (more than once a week) consumption of peanuts or peanut butter during pregnancy by mothers from atopic families is more likely to result in peanut sensitization in the unborn child and should therefore be discouraged.

We confirmed the findings of Tariq et al. (1996), who reported that peanut consumption by mothers during pregnancy (69% of the mothers) and lactation (46%) was relatively high. However, unlike our study, their data showed that maternal nut ingestion during pregnancy and/or lactation did not increase nut sensitization in the offspring (5).

Hourihane et al. (2) found that mothers of younger probands (5-yr-old or younger) were significantly more likely than mothers of older probands (older than 5 yr) to have eaten peanuts regularly (at least weekly) while pregnant or breast feeding. The study carried out by Hourihane et al., as well as the present study, did not control for recall bias (2).

We found no significant differences between the peanut-sensitized and non-peanut-sensitized groups regarding the consumption of peanuts by mothers during lactation. This finding is interesting because atopic mothers are currently advised to avoid peanut ingestion during lactation. Some mothers, however, did report

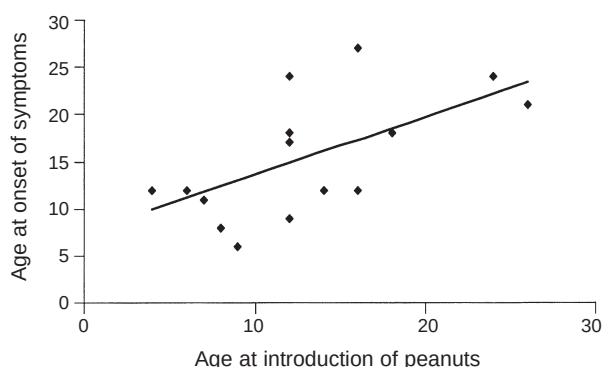


Fig. 1. Correlation, in the peanut-sensitized group, between age at introduction of peanuts with the onset of symptoms. $r = 0.63$, 95% confidence interval (0.19; 0.86).

developing a craving for peanuts during pregnancy. It may well be that the amount of peanut allergens transferred directly into breast milk is variable, and these individual variations should be studied in the future. We noted with surprise that delayed introduction of formula feeding, and thus exclusive breast feeding, did not protect against the development of peanut sensitivity in the infants.

Peanuts or peanut butter was introduced into the child's diet from a younger age in the peanut-sensitized group (at a mean age of 12.5 months) as compared with the control group (mean age of peanut or peanut butter introduction was 17 months). This was significant ($p=0.03$). This result correlates well with that from the study carried out by Tariq et al. (1996), where the mean age at the first recorded exposure to peanuts was 12.6 months (5).

It is believed that the early introduction of peanuts or peanut-containing foods into the atopic child's diet precipitates the clinical onset or manifestation of peanut allergy in an already sensitized infant (1–3, 5).

Our study did not account for the possible inadvertent exposure to peanuts or peanut butter in the child's diet by other caregivers or exposure outside the home.

There was a positive correlation in the peanut-sensitized group between the age of onset of symptoms (age of clinical diagnosis) and the age of first introduction of peanuts or peanut butter into the child's diet. This was not the case for the control group. This suggests that the symptoms reported in the peanut-sensitized children, at the time of clinical diagnosis, could have been directly caused by the introduction of peanuts or peanut butter into the child's diet. Ewan (3) also found that the age at the onset of symptoms

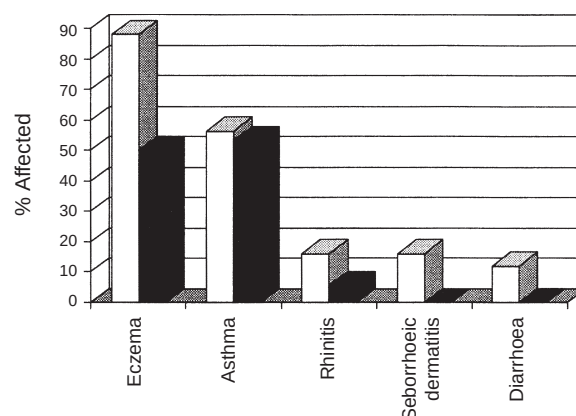


Fig. 2. Profile of symptoms in the peanut-sensitized group (open boxes) compared with the control group (filled boxes). $p = 0.006$.

correlated with early sensitization to peanuts. Because the peanut-sensitized subjects in the present study were sensitized to other foods besides peanuts, the symptoms experienced at the time of diagnosis may be attributed to exposure to other foods to which the child was allergic. This may not have been the case if children with peanut allergy only had been selected as the peanut-sensitive group. The significantly positive association with soya sensitivity was expected because of the known cross-reactivity with peanut allergens. The peanut-sensitized group was also found to be significantly more likely to have positive RAST results for wheat and fish (Table 1), and therefore peanut sensitivity may well be a marker of more extensive IgE-mediated hypersensitivity in small infants.

On clinical examination of the subjects, it was found, as expected in the 0–3-year-old age group, that eczema was the dominant symptom in the peanut-sensitized children (88%). This was followed in frequency by asthma, rhinitis, and seborrhoeic dermatitis. Although these symptoms were present in both study groups, they were significantly more prevalent in the peanut-sensitive group than in the control group (Fig. 2).

Our clinical findings are similar to those of Hourihane et al. (2), Hourihane (4), and Ewan (3). The studies conducted by Tariq et al. (5) and Hourihane et al. (2) showed that peanut allergy was associated with asthma, eczema, and rhinitis. Ewan (3) also reported that asthma was a major clinical feature in the older, peanut-sensitized children (76% of subjects were affected). However, we did not perform food challenge tests to establish a clear causative correlation between the sensitization to peanuts, egg, and milk, and the clinical symptoms observed in our patients. Furthermore, larger and more detailed studies need to be undertaken to characterize the impact of maternal and infant diet on the early onset of the manifestations of peanut allergy.

The identification of local foods and food products that contain peanuts, peanut oil, or hidden extracts of peanuts is essential if the avoidance of peanuts by peanut-allergic individuals is to be effective. The current public knowledge on local foods and food products containing peanuts, peanut oil, or 'hidden' peanut extracts is extremely limited in South Africa. This, in turn, makes it very difficult for peanut-allergic individuals to completely eliminate peanuts from their diet. As peanut allergy tends to be persistent (19) and poses a major risk for anaphylaxis (19, 20), avoidance of

sensitization in high-risk individuals is of vital importance (21, 22).

This study suggests that avoidance of early peanut exposure *in utero* during pregnancy would be a logical recommendation for mothers who have a strong family history of allergies. It is vital to ensure that the patient, family, and any care providers understand how to avoid early exposure to all forms of peanut allergens and the potential consequences of inadvertent ingestion (1–4, 23). Dieticians should work in close co-operation with the medical profession regarding the management of peanut-allergic patients. The counselling of mothers with a strong family history of allergies, in the measures that may be taken to prevent possible sensitization of infants, and the subsequent onset of allergic reactions in such infants, should be encouraged.

References

1. SAMPSON HA. Managing peanut allergy. *BMJ* 1996; 312: 1050–1.
2. HOURIHANE JOB, DEAN TP, WARNER JO. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. *BMJ* 1996; 5: 127–130.
3. EWAN PW. Clinical study of peanut and nut allergy in 62 consecutive patients: new features and associations. *BMJ* 1996; 312: 1074–8.
4. HOURIHANE JOB. Early life origins of peanut allergy. *Curr Allergy Clin Immunol* 1996; 9: 16–21.
5. TARIQ SM, STEVENS M, MATTHEWS S, RIDOUT S, TWISLTON R, HIDE DW. Cohort study of peanut and tree nut sensitisation by age of 4 years. *BMJ* 1996; 313: 514–7.
6. CHANDRA RK, PURI S, SURAIYA C, CHEEMA PS. Influence of maternal food antigen avoidance during pregnancy and lactation on incidence of atopic eczema on infants. *Clin Allergy* 1986; 16: 563–9.
7. ZEIGER RS, HELLER S, MELLON MH, et al. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomised study. *J Allergy Clin Immunol* 1989; 84: 72–89.
8. FAITH-MAGNUSSON K, KJELLMAN NIM. Allergy prevention by maternal elimination during late pregnancy: a 5 year follow-up study. *J Allergy Clin Immunol* 1992; 89: 709–13.
9. ZEIGER RS. Dietary manipulations in infants and their mothers and the natural course of atopic disease. *Pediatr Allergy Immunol* 1994; 5 (Suppl. 6): 33–43.
10. ZEIGER RS, HELLER S. The development and prediction of atopy in high risk children: Follow up at seven years in a prospective randomised study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995; 95: 1179–90.
11. HIDE D, MATTHEWS S, MATTHEWS L, et al. Effect of allergen avoidance in infancy on allergic manifestations at age two years. *J Allergy Clin Immunol* 1994; 93: 842–6.
12. BROWN HM. Allergenic peanut oil in milk formulas. *Lancet* 1991; 338: 1523.

13. MONERET-VAUTRIN DA, HATAHET R, KANNY G. Risks of milk formulas containing peanut oil contaminated with peanut allergens in infants with atopic dermatitis. *Paediatr Allergy Immunol* 1994; 5: 184–8.
14. KEATING MU, JONES RT, WORLEY MS, SHIVELY CA, YUNGIGER JW. Immunoassay of peanut allergens in food-processing materials and finished foods. *J Allergy Clin Immunol* 1990; 86: 41–4.
15. OLSZEWSKI A, PONMS L, MOUTETE F, et al. Isolation and characterisation of protein allergens in refined peanut oil. *Clin Exp Allergy* 1998; 28: 850–9.
16. DE MONTIS G, TRUONG M, TOUSSAINT B, BERMAN D, TOUDOIRE C. Sensibilisation a l'arachide et preparations vitaminiques en solution huileuse. *Arch Pediatr* 1995; 2: 25–8.
17. DE MONTIS G, GENDREL D, CHEMILLIER-TRUONG M, DUPONT C. Sensitisation to peanut and vitamin D preparations. *Lancet* 1993; 341: 1411.
18. DE MONTIS-TRUONG M, TOUSSAINT B, BERMAN D, TOUDOIRE C. L'allergie a la cacahuette, pathologie iatrogene? *Arch Fr Pediatr* 1993; 50: 175.
19. BOCK SA, ATKINS FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 1989; 83: 900–4.
20. ASSEM ESK, GELDER CM, SPIRO SG, BADERMAN H, ARMSTRONG RF. Anaphylaxis induced by peanuts. *BMJ* 1990; 300: 1377–8.
21. YUNGIGER JW, SWEENEY KG, STURNER WQ, et al. Fatal food-induced anaphylaxis. *JAMA* 1988; 260: 1450–2.
22. HOURIHANE JOB, KILBURN SA, DEAN P, WARNER JO. Clinical characteristics of peanut allergy. *Clin Exp Allergy* 1997; 27: 634–9.
23. MORRIS A. A practical guide to suspected food allergy. *Curr Allergy Clin Immunol* 1997; 10: 14–8.