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Influence of maternal diet during lactation and use of formula feeds on development of atopic eczema in high risk infants

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Abstract

***Objective*—To examine the effects of maternal diet during lactation and the use of formula feeds on the development of atopic eczema in infants at risk.**

***Design*—Mothers who planned to breast feed exclusively were randomly allocated to either a restricted diet (avoiding milk and other dairy products, eggs, fish, peanuts, and soybeans) or a diet without restrictions. Mothers who did not plan to breast feed were randomly allocated to using one of three formula feeds.**

***Setting*—Child health centre in Canada.**

***Subjects*—97 Mothers who chose to breast feed and 124 mothers who did not.**

***Interventions*—Restricted diet for 49 mothers who breast fed. Casein hydrolysate formula, soy milk formula, or cows' milk formula for infants not breast fed.**

***Main outcome measure*—Development of eczema in babies.**

***Results*—Infants were followed up over 18 months and examined for eczema. Eczema was less common and milder in babies who were breast fed and whose mothers were on a restricted diet (11/49 (22%) *v* 21/48 (48%)). In infants fed casein hydrolysate, soy milk, or cows' milk 9/43 (21%), 26/41 (63%), and 28/40 (70%), respectively, developed atopic eczema.**

***Conclusions*—In families with a history of atopic eczema mothers who breast feed should avoid common allergenic foods during lactation. If they choose not to breast feed a hydrolysate formula should be used.**

Introduction

Atopic disorders include eczema, asthma, and rhinitis. These are common causes of childhood illness and visits to doctors. The enormous costs, both measurable (visits to the doctor, admissions to hospital, laboratory tests, medicines, special diets) and immeasurable (emotional stress, lost school days, social isolation), of managing children with atopic eczema have led to attempts at prevention. Food allergy, such as hypersensitivity to cows' milk, is an important contributory factor in atopic eczema[1] and occurs commonly during early life.[2] Allergic reactions to foods peak in infancy, and the prevalence tends to decrease with age.[3] Although breast feeding affords partial protection,[4-6] the occurrence of serious atopic disease even among exclusively breast fed children[7,8] prompted us to suggest that sensitisation to food antigens may occur in utero and through breast milk.[9,10] Several data support this concept.[10-13] In view of these observations we conducted a randomised study to evaluate the role of maternal diet during lactation and of special infant formulas in preventing atopic eczema in infants at high risk.

Subjects and methods

In cases in which either of the baby's parents had a family history of atopic disease mothers were asked whether they planned to breast feed exclusively. They were contacted in antenatal clinics or a few days before or immediately after delivery in the two maternity hospitals in the city. About 85% of those eligible agreed to take part in the study. Staff in the labour room and nursery were instructed on the need for ensuring exclusive breast feeding. If the mothers intended to breast feed the study was explained to them, and they were randomised (based on a random number table) into either the experimental or the control group. Those in the experimental group were asked to observe dietary restrictions (exclusion of milk and other dairy products, eggs, fish, peanuts, and soybeans) for six months or the duration of lactation, if shorter than six months. They were advised to take 1 g of calcium supplement daily. Compliance was assessed by examining their daily diaries of foods consumed, direct questioning, and testing by enzyme linked immunoassay (ELISA) for δ lactoglobulin and ovalbumin in random samples of breast milk. Mothers who elected not to breast feed were given one of three coded formulas: conventional cows' milk (Enfalac), soy milk (Prosobee), and casein hydrolysate (Nutramigen). All three formulas are manufactured by Mead Johnson Canada. Formula feed was given on demand and ad libitum. Each infant received the assigned formula for at least six months. A physician examined the infants at 2, 4, 6, 12, and 18 months or more often if asked by the mother. The minimum follow up was 18 months in each case. The mothers and the observer were not aware of the type of formula given.

Atopic eczema was diagnosed if physical examination showed areas of scaly, erythematous, and itchy rash primarily of the face, the scalp, behind the ears, and the flexural folds. An eczema score, based on the system devised by Dr David Atherton, Hospital for Sick Children, Great Ormond Street, London, was calculated.[10] The score is based on the distribution (20 parts of the body), type (erythema, scaling, lichenification), and severity (score 0 to 3) of skin disease. The maximum possible score is 180.

The breast fed and formula fed groups were analysed

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separately owing to the self selection by the mothers. Within each set the mothers were allocated at random to each feeding regimen. To stabilise the variance (SD^2) the square root of the eczema scores were taken before analysis. The two groups who breast fed were compared by Student's one tailed *t* test for transformed eczema scores and by the χ^2 test with Yates's correction for frequencies at $p<0.05$. The three groups who used the formula feeds were compared by Tukey's w procedure for transformed scores and the χ^2 test for frequencies at $p<0.05$.

Results

Eczema was seen less often and was milder in breast fed babies whose mothers were on restricted diets. Table I shows the results as the cumulative incidence up to age 18 months and the maximum eczema score at any point of observation. Of 112 mothers who chose to breast feed, 57 were randomised into the group asked to avoid five common allergenic foods. Eight women who dropped out of the study or breast fed exclusively for less than eight weeks were excluded from analysis. Atopic eczema was diagnosed in 11 out of 49 infants. Of the 55 mothers who were asked to not take any dietary precautions, seven were lost to follow up or stopped breast feeding exclusively before eight weeks and were excluded from analysis. Atopic eczema was seen in 21 out of 48 infants. Moreover, the skin was more severely affected in these 21 infants than in the infants whose mothers were on restricted diets. The two groups were comparable in terms of mean duration of exclusive breast feeding (5·2 (SD 0·8) *v* 5·5 (0·7) months in experimental and control groups respectively) and several other confounding variables (table II).

Among the formula fed infants the incidence of atopic eczema was lowest in those given a casein hydrolysate preparation: nine of 43 infants developed eczema (table III). The incidence of eczema in infants fed soy milk formula did not differ from that in the group fed a conventional cows' milk formula. The eczema score also was lowest in the hydrolysate group (table III). The various formula fed groups did not differ with regard to several confounding variables (table II).

The nutritional state of mothers who took dietary precautions during lactation was comparable with that of the control group as judged by change in body weight, haemoglobin concentration, and serum concentrations of albumin and prealbumin (data not shown).

TABLE I—*Effect of maternal dietary precautions during lactation on the incidence and severity of atopic eczema in their babies*

Group	No of mothers	Mean eczema score of babies	Babies with eczema: No	Babies with eczema: Mean score
Dietary precautions	49	5*	11†	22
No precautions	48	17*	21	34

*Means significantly different ($p<0.05$) based on Student's one tailed *t* test of square roots of scores (SD=4·1).
†Compared with control group, $\chi^2=4.32$, $p<0.05$.

TABLE II—*Baseline characteristics of groups in which babies were breast fed or given formula feeds*

Variable	Mothers who breast fed: Dietary precautions	Mothers who breast fed: No precautions	Mothers who used formula feeds: Cows' milk formula	Mothers who used formula feeds: Soy formula	Mothers who used formula feeds: Casein hydrolysate formula
Mean family income (Canadian $)	30 114	32 865	26 381	24 673	25 995
Maternal education:					
University	12	9	5	5	3
High school	28	30	27	30	34
<High school	9	9	8	6	6
Mean (SD) birth weight (g)	3293 (210)	3180 (246)	3270 (320)	3416 (270)	3370 (195)
Mean (SD) age of babies when solids introduced (months)	5·6 (0·2)	6·0 (0·1)	6·1 (0·2)	6·3 (0·3)	5·8 (0·1)
Pets at home	8	5	10	12	13
Parental smoking	6	8	14	12	16
Day care	23	21	28	20	22
Family history of atopy:					
Both parents	15	12	12	14	11
One parent	34	36	28	27	32
Cord blood IgE >0·7 U/ml†	24/38	21/37	18/32	18/30	16/31

†No positive/No tested

TABLE III—*Effect of special formula feeding on incidence and severity of atopic eczema*

Group	No of babies	Mean eczema score of babies	Babies with eczema: No	Babies with eczema: Mean score
Cows' milk	40	38	28	55
Soy milk	41	36	26	56
Casein hydrolysate	43	6*	9†	31

*Mean score significantly different ($p<0.05$) based on Tukey's w test of square roots of scores (pooled SD=5·2).
†Compared with two other groups, $\chi^2=23.6$, $p<0.005$.

Discussion

Some of the controversies over dietary prevention of atopic eczema can be attributed to differences in the design of various studies and in the analysis of results. These have been discussed elsewhere[14] and are summarised here. Firstly, there are several possible methods of examining the health effects of infant feeding practices, and the advantages of conducting prospective randomised controlled trials are obvious. Secondly, subjects should be stratified based on high or low risk—for example, it would be erroneous to examine the potential effects of breast feeding or special formula feeding on allergic disease in the general population. Instead, separate comparisons should be made for infants at high or low risk depending on the presence or absence respectively of a history of atopic disease in first degree relatives. Thirdly, in retrospective studies the duration of parental recall of events is critical. Even in motivated and cooperative groups of parents' recall of neonatal events one to five years later is prone to error. Fourthly, the sample size should take into account adequate statistical power and the projected rate of drop out. Fifthly, the duration and exclusivity of mode of infant feeding should be determined and defined. Sixthly, criteria for diagnosing outcome events and for grading their severity should be defined. In the case of atopic eczema knowing its severity is as important as recording its incidence. For parents it is easy to cope with a mild rash but it is quite another matter when the infant's skin is extensively affected with frequent extra infections. Seventhly, the outcome events should be assessed by investigators who are blinded to the mode of infant feeding. Finally, all possible confounding variables should be recorded and taken into account when analysing data. These and other epidemiological considerations[15] must be considered when the results of studies are assessed and when further research is planned.

Our prospective studies have shown that breast feeding provides partial protection against atopic eczema in infants for whom there is a history of atopic disease among first degree relatives. The benefit extends well beyond the period of breast feeding and covers atopic disease associated with allergy to a variety of foods. These observations and other data point to the nature of protection attributable to breast feeding, which is non-specific to certain antigens. This benefit is considerably enhanced if the mother avoids common allergenic foods during lactation. Obviously, the nutritional state of the mother should be closely monitored and the women given professional dietary advice.

For high risk infants who are formula fed we

recommend a hydrolysate formula. The incidence and severity of eczema in the infants fed a casein hydrolysate formula were significantly reduced compared with those in infants fed conventional cows' milk or soy milk formulas. The incidence in the hydrolysate group was comparable with that in the breast fed infants whose mothers took dietary precautions during lactation, though the eczema was more severe. The incidence in the hydrolysate group was significantly lower than that in the breast fed group whose mothers were not on a restricted diet. In our prospective randomised study soy milk formula did not offer any preventive advantage in high risk infants, as also reported by others.[16,17]

In conclusion, mothers of infants with a family history of atopy should avoid common allergenic foods while breast feeding. Alternatively, the infants should be fed a milk hydrolysate formula.

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Prognosis in diabetic nephropathy

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Abstract

***Objective*—To assess the effect of long term antihypertensive treatment on prognosis in diabetic nephropathy.**

***Design*—Prospective study of all insulin dependent diabetic patients aged under 50 with onset of diabetes before the age of 31 who developed diabetic nephropathy between 1974 and 1978 at Steno Memorial Hospital.**

***Setting*—Outpatient diabetic clinic in tertiary referral centre.**

***Patients*—Forty five patients (20 women) with a mean age of 30 (SD 7) years and a mean duration of diabetes of 18 (7) years at onset of persistent proteinuria were followed until death or for at least 10 years.**

***Interventions*—Antihypertensive treatment was started a median of three (0-13) years after onset of nephropathy. Four patients (9%) received no treatment, and 9 (20%), 13 (29%), and 19 (42%) were treated with one, two, or three drugs, respectively. The median follow up was 12 (4-15) years.**

***Main outcome measures*—Arterial blood pressure and death.**

***Results*—Mean blood pressure at start of antihypertensive treatment was 148/95 (15/50) mm Hg. Systolic blood pressure remained almost unchanged (slope −0·01 (95% confidence interval −0·39 to 0·37) mm Hg a year) while diastolic blood pressure decreased significantly (0·87 (0·65 to 1·10) mm Hg a year) during antihypertensive treatment. The cumulative death rate was 18% (8 to 32%) 10 years after onset of nephropathy, in contrast to previous reports of 50% to 77% 10 years after onset of nephropathy. As in previous studies, uraemia was the main cause of death (9 patients; 64%).**

***Conclusions*—The prognosis of diabetic nephropathy has improved during the past decade largely because of effective antihypertensive treatment.**

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Introduction

About 35% of patients with insulin dependent diabetes develop persistent proteinuria, a decline in glomerular filtration rate, and increased arterial blood pressure, which collectively constitute the clinical syndrome of diabetic nephropathy.[1-3] Nephropathy is the main cause of the increased morbidity and mortality in insulin dependent diabetics.[1-5] The high mortality is due to an excess of cardiovascular mortality[6] and to end stage renal failure.[1-4] The cost of care for end stage renal disease in the United States currently exceeds $0·8 billion a year for diabetic nephropathy alone, and the amount is rapidly rising.[7] On average, death occurs five to 10 years after the start of persistent proteinuria.[1,2,4]

Several studies dealing with small numbers of patients have shown that effective antihypertensive treatment postpones renal insufficiency in insulin dependent diabetics with nephropathy.[8-12] The beneficial effect of such treatment on the prognosis of insulin dependent diabetic patients with nephropathy has not been elucidated. We therefore studied 45 insulin dependent diabetic patients with onset of diabetic nephropathy between 1974 and 1978, following them until death or for at least 10 years. Ninety one per cent of the patients received antihypertensive treatment.

Patients and methods

All insulin dependent diabetic patients with onset of diabetes before the age of 31 who were referred with proteinuria or who developed persistent proteinuria