Feasibility and Acceptability of a Proposed Infant Feeding Intervention Trial for the Prevention of Type I Diabetes

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OBJECTIVE — To determine the feasibility of a randomized double-blind controlled trial of an infant formula without intact cow's-milk protein for preventing type I diabetes in high-risk children.

RESEARCH DESIGN AND METHODS — We surveyed 83 people who either were parents of a child with type I diabetes or were pregnant women with type I diabetes in the ambulatory diabetes and obstetrics clinics in a university hospital. After a written and verbal description of the cow's milk–diabetes hypothesis, participants were asked to sign a sham consent form. A questionnaire designed to explore factors affecting their decision to either sign or not sign the consent form, as well as infant-feeding patterns, was subsequently administered.

RESULTS — Overall, 69.9% (95% confidence interval, 60.0–79.8%) consented to participation in the proposed randomized trial. The decision to consent was not affected by the degree of belief in the cow's milk–diabetes hypothesis, the child's risk of diabetes, the respondent's demographic data, or infant feeding habits.

CONCLUSIONS — A randomized feeding intervention study is an acceptable and feasible way to determine whether avoidance of cow's-milk protein during the first 6 months of life prevents type I diabetes in North American children.

There is a large body of evidence to support the hypothesis that early exposure to cow's-milk protein in infancy may be causally related to type I diabetes (1). A large international randomized trial to determine whether a formula without cow's-milk protein will prevent diabetes in children who are genetically at risk is therefore in the final planning stages (2). The feasibility and logistics of such a trial have now been successfully tested in a small pilot study of 20 eligible subjects in Finland (H.K. Akerblom, personal communication), in which 20 of 22 (91%) eligible families consented to random assignment of their newborn child to receive one of two formulas (2). The need for estimates of the participation rate in North America, where different attitudes regarding infant nutrition and participation in clinical trials may prevail, warranted this survey of the parents of potential subjects.

RESEARCH DESIGN AND METHODS

— Between 1 September 1993 and 1 May 1994, one research dietitian (J.R.S.) approached 87 subjects in the waiting rooms of the obstetrics and diabetes clinics at Chedoke-McMaster Hospitals to request participation in the survey. All eligible subjects asked to participate were attending the clinics on a day when the research dietitian was present. Two groups of subjects were identified: pregnant women with type I diabetes and one or both parents of a child with type I diabetes.

Of those approached, 95% (83 of 87) participated. Written and verbal information was provided regarding the 20-year risk of type I diabetes in their children, the cow's milk–diabetes hypothesis, and the nature of the planned clinical trial. Participants were asked to imagine that such a trial was recruiting subjects; fathers and nonpregnant mothers of children with diabetes were further asked to imagine that they were expecting another child. They were then asked to sign a consent form if they would enroll a newborn child in the study. All participants were told that this was a sham consent form and that their signature did not commit them to enrollment in a subsequent real study. This form and the subsequent questionnaire were approved by the Chedoke-McMaster Hospitals' ethics committee.

Regardless of whether or not the

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CI, confidence interval.

Table 1—*Characteristics of consenters and those who refused participation in the proposed trial*

	Consenters	Refusers
n (%; 95% CI)	58 (69.9; 59.9–80.0)	25 (30.1; 20–40.1)
Pregnant (%)	19 (32.8)	12 (48.0)
Age	35.5 ± 7.8*	35.5 ± 8.0*
Total children	1.6 ± 1.1†	1.8 ± 1.4†
Children with type I diabetes	0.7 ± 0.6	0.6 ± 0.6†
Belief in hypothesis		
Responding	57	23
Believe	18 (31.6)	11 (47.8)
Unsure	33 (57.9)	10 (43.5)
Disbelieve	6 (10.5)	2 (8.7)

Data are means ± SD or *n* (% or as indicated). Number of missing data: *3; †1. $P > 0.05$ for all.

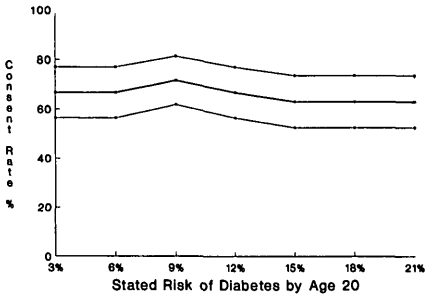

Figure 1—*Changes in the consent rate with different stated risks of diabetes. The effect of quoting different 20-year risks of diabetes on the ease with which respondents either consented or refused to participate in the proposed trial was explored in 81 of 83 respondents. At the time when consent was sought, parents were initially told that a future child's risk of diabetes by age 20 could be as high as 10%; they were subsequently asked to indicate whether their willingness to consent would be different at different risks varying from 3 to 21%. Results are displayed as percent consenting and 95% CIs.*

subjects consented, demographic data, the degree of belief in the study hypothesis, the degree of breast-feeding, and the time of introduction of foods for previous and subsequent children were recorded. The degree to which the newborn's stated 20-year risk of diabetes influenced the decision either to sign or not to sign the consent form was also explored. Subjects were presented with different risks and then asked whether their decision to consent would change.

Statistical analysis

The proportion of respondents signing the consent form and 95% confidence intervals (CIs) were calculated using the Statistix software program (version 4.0, Analytical Software, St. Paul, MN). Consenters' and nonconsenters' responses to questions were compared using the Student's *t*, Mann-Whitney *U*, and χ^2 statistical tests. Paired Student's *t* tests and McNemar's χ^2 statistic were used to compare infant feeding patterns for prior children with patterns anticipated for future children.

RESULTS— The 83 participants included 31 pregnant women and 52 nonexpecting parents of a child with type I diabetes. The four nonparticipants cited a desire to discuss the issue with an absent father and/or the lack of time to complete the questionnaire as reasons for not participating.

Consent was obtained from 19 of 31 pregnant respondents (61.3%; 95% CI, 44.2–78.4%) and 39 of 52 nonpregnant respondents (75%; 95% CI 63.2–86.8%). Because there was no difference between the consent rates of the pregnant respondents versus those of the nonpregnant respondents ($\chi^2 = 1.73$; $P = 0.2$), the remaining analyses compared all consenters with all nonconsenters.

Overall, 58 of 83 respondents consented to participate in the proposed randomized trial (69.9%; 95% CI 60.0–79.8%). Subjects who consented were similar to nonconsenters with respect to age, parity, and number of children with type I diabetes (Table 1).

The degree of belief in the cow's milk–diabetes hypothesis was similar in the two groups (Table 1): 89.5% of consenters and 91.3% of nonconsenters either believed the hypothesis or were undecided ($P > 0.05$). Patterns of breast-feeding and introduction of dairy and other products into the diet of previous and future children were also similar (all $P > 0.05$). Of the 25 nonconsenters, 15 provided a reason: three were reluctant to expose their child to a cow's milk–based formula, seven wanted to choose their own formula, four cited the inconvenience of participation, and one wanted further information.

Participants' refusal or consent was not affected by the 20-year risk of diabetes in their newborns; it did not change even when the quoted risk of diabetes was varied from 3 to 21% (Fig. 1).

Most respondents indicated that future infants would be breast-fed for a longer period of time than previous infants ($P < 0.0001$) had been and would have less formula supplementation ($P = 0.01$). Of 55 consenters, 87.3% (95% CI 78.5–96.1%) indicated that their next child would be breast-fed (compared with 71.7% for a previous child) and 32.7% (95% CI 19.9–45.5%) anticipated that breast-feeding would occur for at least a few months; 29.6% (95% CI 17.4–41.8%) of 54 consenters anticipated that exclusive breast-feeding would occur for a variable time period. Only 5.6% (95% CI 0–11.7%) anticipated exclusive breast-feeding for at least a few months (Table 2).

CONCLUSIONS— This survey found that 70% of respondents would enroll their newborn child in a feeding intervention trial to determine whether early avoidance of cow's milk prevents type I diabetes. This manner of estimat-

Table 2—*Breastfeeding plans for next child (consenters only)*

Breast-feeding duration	Anticipated Degree of Formula Supplementation		
	No formula use	Some formula use	Regular formula use
Less than a few weeks			
%	0	0	14.8
n	—	—	8
95% CI	—	—	5.3–24.3
A few months			
%	5.6	18.5	7.4
n	3	10	4
95% CI	0–11.7	8.2–28.9	0.4–14.4
Unspecified duration			
%	24.1	27.8	1.9
n	13	15	1
95% CI	12.7–35.5	15.8–39.7	0–5.4

Fifty-four of 58 consenters answered the two questions regarding both breast-feeding duration and formula use.

ing the consent rate; the fact that respondents did not change their minds after consent was either obtained or refused, even after factors affecting their willingness to consent were explored; and the high survey participation rate (95% of all eligible people attending the clinics on days when the research dietitian was present) suggest that 70% is a reliable and unbiased estimate of the consent rate.

No relationship was found between the decision to consent and belief in the cow's milk–diabetes hypothesis, the child's risk of diabetes, the respondent's demographic data, or infant feeding habits. Indeed, spontaneous comments offered by nonconsenters suggested that discomfort with the random allocation process or concerns regarding neonatal cow's-milk exposure were the main reasons for not signing the consent form.

Absence of a relationship between willingness to consent and the quoted baseline risk of diabetes suggests that respondents did not make their decisions on the basis of a particular degree of risk. This is consistent with research showing that subjects based decisions to participate personally in clinical trials on factors other than risk of disease (3).

Because of publicity in the lay press regarding the cow's milk–diabetes hypothesis, mothers with a family history of diabetes might increase the amount or exclusivity of breast-feeding to protect their infant from exposure to any study formula in a clinical trial. Indeed, most respondents did anticipate higher breast-feeding rates for future than for previous children. Nevertheless, only 5% of consenting respondents anticipated exclusive breast-feeding for at least a few months. This is consistent with the Finnish pilot study in which only 1 of 20 randomly assigned infants of mothers with type I diabetes was exclusively breast-fed for 6 months (H.K. Akerblom, personal communication). It is also consistent with observations that mothers with type I diabetes supplement breast-feeding with formula earlier than mothers without diabetes (4,5), despite intentions to breast-feed at the same rate (6). Thus almost all infants enrolled in the planned feeding intervention trial would be exposed to the randomly allocated study formula.

The results of this survey indicate that a randomized feeding intervention trial in infants is both highly acceptable and feasible and that despite widespread publicity regarding the cow's milk–diabetes hypothesis, adults at highest risk of having children with type I diabetes are reserving judgment as to the actual cause.

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