

Perinatal and Neonatal Determinants of Childhood Type 1 Diabetes

A case-control study in Yorkshire, U.K.

PATRICIA A. MCKINNEY, PHD
ROGER PARSLAW, MSC
KAREN A. GURNEY, PHD

GRAHAM R. LAW, PHD
H. JONATHAN BODANSKY, MD
RHYS WILLIAMS, FFPHM

OBJECTIVE — To identify environmental factors that exert their effect in the perinatal and neonatal period and influence the subsequent onset of insulin dependent (type 1) diabetes during childhood.

RESEARCH DESIGN AND METHODS — A population-based case-control study of data abstracted from the hospital obstetric and neonatal records of 196 children with type 1 diabetes and 325 age- and sex-matched control subjects. Analysis of matched sets by conditional logistic regression was conducted for a range of perinatal and neonatal factors.

RESULTS — A significantly raised risk was observed for illnesses in the neonatal period (OR 1.61, 95% CI 1.06–2.44), the majority of which were infections and respiratory difficulties. Exclusive breast feeding as the initial feeding method was significantly protective (OR 0.65, 95% CI 0.45–0.94). There were no significant associations with high- or low-birth weight, being firstborn or small-for-dates. All factors significant (5% level) for the entire dataset, that is, maternal age, type 1 diabetes in mothers, preeclampsia, delivery by cesarean section, neonatal illnesses, and initial breast feeding were modeled and the OR remained significant for all variables other than cesarean section.

CONCLUSIONS — The findings are based on medical record data that cannot be subject to biased recall of mothers. Neonatal illnesses increased and initial breast feeding decreased the risk of childhood type 1 diabetes. Further determinants of risk are mothers with type 1 diabetes, older mothers, and preeclampsia during pregnancy.

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It is becoming increasingly well-recognized that the intrauterine and neonatal environment are influential in determining future patterns of disease (1), and evidence is accruing in relation to childhood diabetes (2,3). Thus, the pathogenic process of autoimmune β -cell destruction may well be initiated in utero or around the time of birth when the developing fetus and neonate are particularly vulnerable and the immune system remains immature.

This population-based case-control study has investigated a comprehensive range of factors relating to perinatal and neonatal experiences recorded in the maternity, delivery, and neonatal hospital records of mothers interviewed on a case-control study of type 1 diabetes. The results represent the second phase of an investigation covering intra-uterine development through to early neonatal life with influences occurring in utero already published

(4). Many putative risk determinants have been investigated for the first time, in addition to looking at factors previously identified in other studies.

RESEARCH DESIGN AND METHODS

The study, using standard case-control methodology (5), received approval from the 17 Local Research Ethics Committees in the study region. Incident cases included those diagnosed with type 1 diabetes over a 2-year period (1993–1994) and taken from the population-based Yorkshire Childhood Diabetes Register (YCDR), which registers cases diagnosed under 16 years of age. All children lived within the former Yorkshire Regional Health Authority at the time of diagnosis. The register ascertained children from three independent sources and was estimated to be 97% complete (6). Permission was given by treating hospital clinicians to approach parents and request their participation.

Two control subjects per case, matched by sex and age (by calendar year of birth and month of birth), were randomly selected from the primary care registrations of the Family Health Service Authority (FHSA) of the matched case (see McKinney et al. [4]). Mothers were interviewed face to face and signed consent given for abstraction of the mother's and her child's medical notes. Table 1 shows the numbers of cases and control subjects who were interviewed and for whom notes were also abstracted with details of missing sets. Participation rates for the interview study were 93.6% and 81.9% for case and control mothers, respectively, and 78% of control subjects were first choice and 18% second choice (4).

A highly structured standard form, previously validated in other studies (7,8), was used by a trained midwife to record a wide range of obstetric, delivery, and neonatal details (4). Events in the early neonatal period were noted with reference to separate neonatal notes if necessary and episodes were recorded up until the date of discharge from hospital. Illnesses and congenital malformations were coded using the *International Classification of Diseases*, version 10 (ICD-10) (9) and drugs using

From the Paediatric Epidemiology Group (P.A.M., R.P.), the Leukaemia Research Fund Centre (K.A.G., G.R.L.), the Diabetes Centre (H.J.B.), The General Infirmary at Leeds; and the Nuffield Institute for Health (R.W.), University of Leeds, Leeds, U.K.

Address correspondence and reprint requests to P.A. McKinney, Director, Paediatric Epidemiology Group, Leeds University, 32 Hyde Terrace, Leeds, LS2 9LN, U.K. E-mail: p.a.mckinney@leeds.ac.uk.

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Abbreviations: ICD-10, International Classification of Diseases, version 10; OR, odds ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Profile of study sample including the frequency of cases and control subjects, medical note abstractions, and matched case-control sets included in the study

	Cases	Control subjects
Interviewed plus notes abstracted	202 (91.8)	354 (81.8)
Interviewed only	18 (8.2)	79 (18.2)
Reason for interview only		
Birth location untraced	0 (—)	5 (0.4)
No maternal consent	1 (5.6)	5 (0.4)
Notes untraced	17 (94.4)	57 (72.1)
Not sought	0 (—)	12 (15.2)
Subtotal (interviewed only)	18 (—)	79 (—)
Total number registered	220 (—)	433 (—)
Matching of sets for analysis		
No match available (excluded)	6 (—)	29 (—)
Case plus 1 control (pairs)	67 (—)	67 (—)
Case plus 2 control subjects (triplets)	129 (—)	258 (—)
Total	202 (—)	354 (—)

Data are n (%).

the framework of the prescription manual the British National Formulary (10). Illnesses and drugs were grouped a priori into categories to allow sufficient numbers for analysis (available from authors on request). Assigning centiles for birth length, birth weight, and head circumference was carried out using a single set of centile charts issued in 1995: these provided a standard measure to facilitate the comparison of cases and control subjects. Medical records came from 17 maternity hospitals within the study region, and for the 12.9% of births occurring elsewhere in the U.K. and abroad, records were received by post.

Statistical analysis of matched case-control pairs and triplets was conducted using Stata (11). Odds ratios (ORs) with exact 95% CI and *P* values were calculated using conditional logistic regression with a single term in the model for univariate estimates. Variables significantly associated with disease obtained from the analysis of individual variables were modeled together in a multivariable analysis. In utero risk factors identified previously (4) were included as a priori control factors. Six cases and 29 control subjects had no matching control subjects or cases and were lost to the matched analysis of 196 sets (129 triplets and 67 pairs) (Table 1).

RESULTS— The distribution of cases included in the analysis is shown by age-group and sex in Table 2. The ethnicity of the majority of both cases (94.9%) and control subjects (95.7%) was white, with 8 cases (4.1%) and 10 controls (3.1%) originating from India or Pakistan.

A range of variables were investigated, and Table 3 gives OR with accompanying 95% CI and levels of significance. The results for length of gestation, small-for-dates, and parity have been published previously (4) but are included for completeness. The results show two statistically significant ORs with the recording in the obstetric or neonatal notes of how the infant was first fed showing a protective effect for exclusive breast feeding. There was a raised OR related to post delivery neonatal illnesses, which were mainly accounted for by infections (ICD-10 P35-P39) (29.9%) and respiratory difficulties (ICD-10 P20-P29) (47%) of which half (52.4%) were unspecified birth asphyxia. The risk did not increase with the number of illnesses, that is, no dose response was present. The hematological disorders included one case with rhesus incompatibility (ICD-code P550). Adjustment of the significant ORs noted above for mothers with type 1 diabetes did not alter the magnitude or the significance of the risk. Patterns of hospitalization did not differ significantly between cases and control subjects; 29.0% of cases and 31.2% of control subjects spent 2 days or less in the hospital, and the mean length of stay was 5.5 and 5.2 days for cases and control subjects, respectively.

Various factors have been associated, both from our own and other studies, with increasing or decreasing risk for childhood type 1 diabetes. Variables significant at the 5% level in a univariate analysis in our study were mother's age (<25, 25–35,

>35), type 1 diabetes mothers, preeclampsia, delivery by cesarean section (4), neonatal illnesses, and breast feeding. These potential explanatory variables were modeled together and the results in Table 4 show they all retained their significance apart from cesarean section and the eldest mothers (>35 years), although the latter was of borderline significance (*P* = 0.06). The addition of neonatal illnesses and breast feeding significantly improved the model fit (likelihood ratio test, χ^2 9.96, *P* = 0.007).

CONCLUSIONS— In an effort to identify nongenetic determinants for childhood type 1 diabetes in utero, perinatal and neonatal exposures have been investigated for potential associations for over 2 decades. However, there are few risk factors that appear consistently across studies. This may reflect different study designs and/or low statistical power to detect risks, the fact that childhood type 1 diabetes is a multifactorial disease making it difficult to isolate individual factors, or the failure to incorporate a measure of genetic susceptibility into the study.

The population-based Yorkshire Children's Diabetes Register (6) was the sampling frame for children with type 1 diabetes on the current study. The case-control study collected interview information from the mothers of a high proportion of case children (93.6%), of which 91.8% had their hospital obstetric records abstracted. There was no reason to suspect that any selection bias was present in relation to the mothers whose notes were abstracted as there were no temporal, geographical case control biases in relation to the unobtainable notes. At the termination of the data collection phase, a slightly lower proportion of control mothers remained without obstetric data, however, only six cases had no matched control and were excluded from the analysis, which ensured the power of the study was retained.

Table 2—Age and sex distribution of cases included in the analysis

	Men	Women
Age range (years)		
0–4	18 (16.8)	22 (24.7)
5–9	35 (32.7)	31 (34.8)
10–15	54 (50.5)	36 (40.4)
Total	107 (100.0)	89 (100.0)

Data are n (%).

Table 3—Perinatal and neonatal risk factors

Factor	Cases	Control subjects	OR (95% CI)
<i>n</i>	196	325	—
Parity of mother†			
First pregnancy	61 (31.1)	115 (35.4)	0.82 (0.56–1.19)
Birth order			
First baby	81 (41.3)	141 (43.4)	0.91 (0.64–1.31)
Length of gestation†			
≤37 weeks	24 (12.2)	35 (10.8)	1.21 (0.69–2.10)
Small-for-dates†			
<10th centile	6 (3.1)	7 (2.2)	1.63 (0.54–4.68)
Birth weight‡			
2,500 to <3,500 g	113 (58.5)	187 (58.1)	1.00 (—)
<2,500 g	11 (5.7)	23 (7.1)	0.89 (0.41–1.92)
≥3,500 g	69 (35.8)	112 (34.8)	1.01 (0.68–1.51)
Head circumference‡			
4th–96th centiles	127 (85.8)	199 (85.0)	1.00 (—)
≤3rd centile	9 (6.1)	17 (7.3)	1.13 (0.43–3.01)
≥97th centile	12 (8.1)	18 (7.7)	1.19 (0.53–2.69)
Birth length‡			
4th–96th centiles	71 (64.8)	126 (68.8)	1.00 (—)
≤3rd centile	11 (9.1)	10 (5.5)	2.09 (0.67–6.45)
≥97th centile	39 (32.2)	47 (25.7)	1.29 (0.71–2.34)
Time to first gasp or cry			
>1 min	24 (7.4)	19 (9.7)	1.38 (0.73–2.60)
Time to regular respiration			
>1 min	11 (5.6)	17 (5.2)	1.15 (0.52–2.55)
Apgar score at minute‡			
Normal 7–10	168 (85.7)	287 (88.3)	1.00 (—)
Moderate 4–6	25 (12.8)	31 (9.5)	1.32 (0.76–2.31)
Severe 0–3	3 (1.5)	7 (2.2)	0.77 (0.19–3.02)
Admission to special care baby unit	31 (15.8)	32 (9.9)	1.65 (0.97–2.79)
Neonatal illnesses			
≥1	61 (31.1)	73 (22.5)	1.61* (1.06–2.44)
Specific illnesses			
Infections	18 (9.2)	22 (6.8)	1.47 (0.75–2.90)
Respiratory disorders	30 (15.3)	33 (10.2)	1.55 (0.90–2.65)
Hematological disorders	6 (3.1)	3 (0.9)	3.48 (0.86–14.08)
Congenital malformations			
≥1	6 (3.1)	18 (5.5)	0.46 (0.17–1.26)
Jaundice	58 (29.6)	80 (24.6)	1.30 (0.86–1.96)
Neonate treated by phototherapy	11 (5.6)	16 (4.9)	1.13 (0.49–2.57)
Neonatal drugs given			
≥1	20 (10.2)	34 (10.5)	0.96 (0.54–1.70)
Specific drugs			
Anti-infectives	14 (7.1)	18 (5.5)	1.36 (0.65–2.83)
Antagonists for central and respiratory system depression	6 (3.1)	14 (4.3)	0.62 (0.23–1.70)
Neonatal X-rays			
≥1	3 (1.5)	7 (2.2)	0.68 (0.17–2.68)
Neonatal scans			
≥1	2 (1.0)	2 (0.6)	1.41 (0.19–10.34)
Other neonatal investigations			
≥1	18 (9.2)	18 (5.5)	1.68 (0.84–3.33)
Initial exclusive breast feeding	73 (37.2)	151 (46.5)	0.65* (0.45–0.94)

Data are *n* (%) or OR (95% CI). *Significant at *P* < 0.05; †previously published (4); ‡cases and control subjects with missing values were excluded from the analysis of continuous variables.

In case-control studies, information reported at the interview may be subject to recall bias, but a major advantage of the current study was the fact the information in the obstetric and neonatal records would be entirely independent of case-control status, thus avoiding the traditional criticism of recall bias. In addition, the obstetric, delivery, and neonatal notes were scrutinized and abstracted by one trained research midwife who was unaware of case-control status and could not therefore introduce bias at the stage of recording data. As an historical set of data spanning 20 years, the availability and quality of the notes and the information they contained was generally very good.

The majority of (4,12–17) but not all (18–20) previous studies have observed an association between childhood type 1 diabetes and older mothers. Because this may represent a real association, although the evidence is not conclusive, its effect was addressed in the current study with the finding of an overall positive association with older mothers. The eldest category, those ≥35 years, carried a twofold risk that was of borderline significance in the multivariate model.

Extensive study of birth weight and size has established a relationship between low birth weight and future risk of developing type 2 diabetes, and mechanisms have been postulated to explain this (21). However, the picture is not so clear for type 1 diabetes, where links to birth weight have been with small-for-dates babies (22) and both heavier (23) and lighter babies (24), whereas others have found no association (19,18,16,20). The current study failed to observe any association with either high- or low-birth weight or small-for-dates babies (4) suggesting that neither absolute weight, maturation at birth, or birth size are factors that strongly predict the occurrence of childhood type 1 diabetes.

The protective effect of breast feeding seen in this study has a somewhat limited interpretation as it relates to information recorded in the obstetric or neonatal notes and is therefore restricted to the time period immediately after birth. However, it supports and adds some weight to the observations of other epidemiological studies (12,16,20) demonstrating a beneficial effect of breast feeding. However, the controversy remains as to whether the apparent protection afforded by breast milk merely reflects the later introduction of cows' milk (25), whose proteins are candidate risk factors for

Table 4—Multivariate analysis of significant prenatal and perinatal risk factors

Factors in the model	Cases	Control subjects	OR (95% CI)
<i>n</i>	196	325	
Mother's age†			
25–35 years	123 (62.8)	182 (56.0)	1.69* (1.11–2.60)
>35 years	20 (10.2)	22 (6.8)	2.07 (0.97–4.43)
Mother with type 1 diabetes†	4 (2.0)	0 (0)	∞ (—)
Preeclampsia†	44 (22.5)	49 (15.1)	1.60* (1.01–2.54)
Cesarean delivery†	34 (17.4)	35 (10.8)	1.45 (0.82–2.55)
Neonatal illnesses			
≥1	61 (31.1)	73 (22.5)	1.55* (1.00–2.42)
Initial exclusive breast feeding	73 (37.2)	151 (46.5)	0.60* (0.41–0.89)

Data are *n* (%) or OR (95% CI). *Significant at $P < 0.05$; †previously published (4). ∞ signifies an infinite odds ratio.

childhood diabetes. Recent results from animal, immunological, and epidemiological studies have failed to provide conclusive evidence associated with the milk protein bovine serum albumin, but beta casein is an interesting new candidate (26). Further research is still required to firmly establish cows' milk as an environmental pathogen for type 1 diabetes.

A number of studies (13,14,27) have shown a raised risk for first pregnancies and firstborn children, with early onset disease possibly being most affected (14). The hygiene hypothesis postulates that immunological isolation in infancy may predispose to later development of type 1 diabetes and that early exposure to infections is protective (28,29). One of the possible predictions of this hypothesis is an increased risk for firstborn children as shown by Wadsworth et al. (19), but our results along with others (18,22) find no excess of type 1 diabetes in firstborns. However, this does not necessarily refute the hypothesis because the complexity of exposure to infections cannot be measured by a single variable.

Mothers with type 1 diabetes confer increased risk of the condition to their offspring (14,30), and we confirmed this.

A new finding was the recording of neonatal illnesses being significantly greater for cases compared with control subjects. Mothers with type 1 diabetes or with preeclampsia are more likely to have their babies more closely observed and monitored after delivery, so increased levels of observation might account for the excess of illnesses seen in the baby. However, there were only four mothers with type 1 diabetes, and adjustment for maternal conditions in the model did not remove the statistical significance of neonatal illnesses. The association for these nongenetic expo-

sure remains an important one but it is difficult to explain biologically because the range of illnesses was fairly broad, no single condition accounted for the risk, and there was no dose response. It may be that the range of neonatal conditions are a proxy measure for an as yet unidentified risk factor.

A significant excess of case children in association with preeclampsia in pregnancy has been observed in our own (4) and two other studies (20,30); one study failed to show an effect (14). The increased risk in the Yorkshire study was unaffected by controlling for neonatal illnesses and other factors, and the results like those of Jones et al. (20) could not be biased by maternal recall. Preeclampsia may be the expression of an immune response of the mother to the fetus and therefore represent early fetal exposure to immune modulation that predisposes to later type 1 diabetes.

In conclusion, early neonatal illnesses are positively associated with increasing risk of type 1 diabetes developing during childhood. Breast feeding immediately after birth is protective. A combined analysis of both prenatal and perinatal factors investigating potential confounding showed adverse intrauterine conditions, particularly preeclampsia, as well as maternal factors, that is, mother's age and the presence of type 1 diabetes are also important determinants of risk.

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