Perinatal Risk Factors for Childhood Type 1 Diabetes in Europe

The EURODIAB Substudy 2 Study Group

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OBJECTIVE — To explore whether perinatal factors are associated with the development of childhood type 1 diabetes.

RESEARCH DESIGN AND METHODS — We studied hospital records from 892 cases of childhood type 1 diabetes compared with 2,291 population-based control subjects in seven study centers in Europe.

RESULTS — In a pooled analysis incorporating stratification by center, we confirmed the previous findings that older maternal age, maternal preeclampsia, neonatal respiratory disease, and jaundice caused by blood group incompatibility are significant risk factors for type 1 diabetes, whereas being a firstborn child, having a low birth weight, or having a short birth length were protective. Cesarean section delivery and neonatal infectious diseases were not significantly associated with the risk of type 1 diabetes in this study. The strongest association was found for blood group incompatibility (AB0 and Rh factor) with an odds ratio (OR) of 2.96 (95% CI 1.88–4.65). AB0 incompatibility (OR = 3.92) was a more common and also a stronger risk factor than Rh incompatibility (OR = 1.62). The effect of AB0 blood group incompatibility was independent of treatment effects in logistical regression analysis.

CONCLUSIONS — Different perinatal events are associated with an increased risk of type 1 diabetes. The effect of maternal-child blood group incompatibility is strong and indicates a true effect that must be further explored.

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The incidence of childhood-onset type 1 diabetes is rapidly increasing in many parts of the world (1,2), particularly in young-onset cases (3–5). A similar finding was noted when incidence trends from 1989 to 1994 were compared in more than 40 centers in Europe (6). Such rapid increases over time cannot be explained by an increase in the genetic predisposition to type 1 diabetes but rather are more likely a result of changes in environmental risk factors that initiate the disease process. For young-onset cases, events that initiate the slowly progressing autoimmune process that leads to diabetes may well occur in the fetal or perinatal period of life.

The most compelling example of an environmental risk factor strongly associated with type 1 diabetes is rubella virus infection occurring during fetal life (7). More recently, fetal exposure to enteroviruses has also been associated with the risk of type 1 diabetes (8–10). Another risk factor that has been found to be strongly associated with type 1 diabetes is isoimmunization due to blood group incompatibility (11). In addition, less specific perinatal factors that have weaker associations with the risk of type 1 diabetes include maternal age (11–16), preeclampsia (11,16,17), cesarean section delivery (11,15–17), birth weight (18), gestational age (11), and birth order (12,15).

The EURODIAB Substudy 2 is a large multicenter case-control study that aims to identify exposures operating early in life that are associated with childhood-onset type 1 diabetes. The eight participating centers represent a large range of type 1 diabetes incidence and health care policies (e.g., delivery practices and vaccination programs). Our study therefore is an opportunity to investigate whether risk factors previously identified in specific populations are also operating in different European countries and to identify exposures that may be too common or too rare in specific populations to detect.

In this report from the EURODIAB Substudy 2, we analyzed perinatal risk factors studied in hospital records from 892 cases of childhood type 1 diabetes compared with 2,291 population-based control subjects by focusing on the mother's pregnancy and the child's perinatal history.

RESEARCH DESIGN AND METHODS

— A total of eight centers with population-based childhood-onset diabetes registers developed according to the standards of EURODIAB ACE (Aetiology of Childhood Onset Diabetes on an Epidemiological Basis) (18) participated in Substudy 2: Austria, Latvia, Lithuania, Luxembourg, Romania, Bulgaria, Northern Ireland, U.K., and Leeds, U.K. Seven of the centers (except Romania) had access to abstractable data from obstetrical records that could identify the perinatal variables under investigation. Altogether, 1,093 cases of diabetes with onset before age 15 years and 3,264 population-based control subjects selected with an age distribution comparable with that of the diabetes cases were invited to participate. Of the

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Abbreviations: OR, odds ratio.

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

Table 1—*Summary of participants in the seven study centers*

Center	Years of case registration	Cases			Control subjects			
		n	Response rate (%)	Availability of obstetrical records (%)	Source of control sample	*n*	Response rate (%)	Availability of obstetrical records (%)
Austria (Vienna)	1989–1994	117	88.9	81.7	Schools	477	79.7	85.3
Bulgaria (west)	1991–1994	176	72.7	99.2	Schools and policlinics	562	78.6	99.5
Latvia (one region excluded)	1989–1994	143	98.6	94.3	Population register	410	79.0	92.9
Lithuania	1989–1994	124	94.4	90.4	Policlinics	369	72.9	98.9
Luxembourg	1989–1995	59	100.0	98.3	Preschools and schools	188	94.7	98.9
U.K. (Leeds)	1993–1994	234	88.9	96.6	General practitioner register	535	76.4	82.2
U.K. (Northern Ireland)	1990–1992	240	78.8	98.9	General practitioner register	723	64.3	97.2
Overall		1,093	86.6	94.3		3,264	75.6	92.9

1,093 cases, 946 (86.6%) were willing to participate, and for 892 of them (94.3%), obstetrical records were accessed (81.6% of the eligible cases). Altogether, 2,467 of the 3,264 eligible control subjects (75.6%) participated, and for 2,291 (92.9%) of them, obstetrical records were available (70.2% of all eligible control subjects). The study base was temporally and geographically well defined for each country, and the procedure for the selection of population-based control subjects was designed in collaboration with the study coordinators in the individual centers (see APPENDIX) according to local circumstances. Details of case and control ascertainment and nonresponse rates in different countries are shown in Table 1.

To maintain uniform standards between centers, local study leaders received detailed written instructions for selection of control subjects, definition of obstetrical and neonatal variables, and completion of the record sheet. In addition, two workshops were organized, and all centers were visited by the study coordinators to ensure uniformity of data collection procedures. The core variables were transferred from the obstetrical records into a standardized coding sheet and were computerized centrally. Details of hospital record data and definitions can be obtained on request. Each study center leader obtained permission from the local ethics committee when one existed. All centers were instructed to adhere to a common informed consent procedure.

The Mantel-Haenszel approach was used to give a pooled odds ratio (OR) that was stratified by center and to provide a test for heterogeneity in the OR from center to center. To adjust for confounders, logistical regression analysis was used with additional terms included in the logistical model to represent centers. Statistical analysis was performed by using the SPSS (Chicago) and STATA (College Station, TX) packages.

RESULTS — In Table 2, the pooled ORs and CIs are given for the core perinatal risk factors studied. Maternal age >25 years (i.e., above the median of control subjects), preeclampsia, neonatal respiratory disease, and jaundice were associated with an increased risk of type 1 diabetes. A low birth weight, a short birth length, and being a firstborn child were protective, whereas no significant effects were detected for gestational age <38 weeks, cesarean section, or being small for gestational age (according to local standards). An increase in risk was noted for children with jaundice, and this association was further elaborated as described below.

Jaundice by cause

The breakdown of causes of jaundice is given by center in Table 3. Comparing jaundice caused by any blood group incompatibility with no jaundice resulted in a Mantel-Haenszel OR of 2.96 (95% CI 1.88–4.65, $P < 0.001$). When specifically examining AB0 incompatibility, the Mantel-Haenszel OR was significantly increased (3.92). For Rh incompatibility, the OR was also increased (1.62) but was not statistically significant. A significant OR (1.27) was also obtained for jaundice of other or unknown causes. This finding may reflect undiagnosed blood group incompatibilities in some centers. In contrast with the heterogeneity evident in the analysis of jaundice reported in Table 2, there was no

Table 2—*Mantel-Haenszel pooled ORs and 95% CIs for the core perinatal risk factors studied*

	OR (95% CI)	*P* value
Maternal age >25 years	1.30 (1.16–1.52)	<0.001
Preeclampsia	1.51 (1.17–1.96)	0.002
Birth order (first vs. other)*	0.86 (0.74–1.00)	0.05
Cesarean section	1.11 (0.87–1.43)	0.40
Gestational age (<38 weeks)	1.03 (0.77–1.37)	0.84
Low birth weight (<2,500 g)	0.44 (0.26–0.76)	0.002
Short birth length (<50 cm)	0.71 (0.57–0.89)	0.003
Small for gestational age (<10th percentile)	1.02 (0.75–1.40)	0.89
Neonatal infectious disease	1.13 (0.82–1.55)	0.47
Neonatal respiratory disease	1.49 (1.04–2.13)	0.03
Jaundice*	1.44 (1.19–1.75)	<0.001

Data are ORs (95% CIs). *Risk associated with these factors showed evidence of heterogeneity ($P < 0.05$) from center to center.

Table 3—*Breakdown of jaundice by cause in each center with pooled ORs relative to children with no jaundice*

Center	*n*	No jaundice	Causes of jaundice: AB0 incompatibility	Rh incompatibility	Other or unknown
Austria					
Control subjects	318	233 (73)	19 (6)	6 (2)	60 (19)
Cases	82	48 (59)	13 (16)	2 (2)	19 (23)
Bulgaria					
Control subjects	438	360 (82)	5 (1)	4 (1)	69 (16)
Cases	126	103 (82)	2 (2)	1 (1)	20 (16)
Latvia					
Control subjects	290	273 (94)	2 (1)	6 (2)	9 (3)
Cases	127	106 (84)	12 (9)	5 (4)	4 (3)
Lithuania					
Control subjects	263	230 (88)	2 (1)	0 (0)	31 (12)
Cases	114	104 (91)	2 (2)	0 (0)	8 (7)
Luxembourg					
Control subjects	176	157 (89)	1 (1)	0 (0)	18 (10)
Cases	57	45 (79)	1 (2)	1 (1)	10 (18)
U.K. (Leeds)					
Control subjects	308	233 (76)	1 (0)	1 (0)	73 (24)
Cases	166	109 (66)	1 (1)	0 (0)	56 (34)
U.K. (Northern Ireland)					
Control subjects	373	247 (66)	0 (0)	1 (0)	125 (34)
Cases	155	96 (62)	0 (0)	0 (0)	59 (38)
Mantel-Haenszel pooled OR (95% CI)		1.00	3.92 (2.28–6.74)	1.62 (0.72–3.67)	1.27 (1.03–1.56)

Data are *n* (%) or ORs (95% CIs).

evidence of heterogeneity between centers when the analyses were performed separately for each of the three causes.

Blood group incompatibility by treatment

In a stratified analysis examining a possible treatment effect in jaundice cases without a diagnosis of blood group incompatibility, treatment versus nontreatment had an OR of 1.48 (0.94–2.33, $P = 0.09$), which suggests a tendency for an increased risk.

In a logistical regression model (Table 4), assessing any possible role of jaundice treatment that allows for the possible confounding effects of the cause of jaundice and center effects, jaundice caused by AB0 blood group incompatibility remained a strong and independent risk factor. The OR for treatment was elevated but did not attain statistical significance.

Age effects

The increased risk associated with blood group incompatibility was seen in all age-at-diagnosis groups (0–4, 5–9, and 10–14 years) with a tendency toward higher ORs in the age-group 5–9 years: 2.31 (0.90–5.96), 3.96 (1.99–7.85), and 2.47 (1.11–5.48), respectively.

Multivariate analysis of perinatal risk factors

Because many of the perinatal risk factors may confound one another, we used a logistical regression analysis to study the independent effects of the different risk factors included in Table 2. The results shown in Table 5 clearly demonstrate that the strongest independent risk factor was AB0 incompatibility.

CONCLUSIONS — This study confirms that perinatal factors are associated with the risk of type 1 diabetes. The pooled analyses in our multicenter study of seven different populations in Europe confirm previous reports that preeclampsia and neonatal respiratory distress confer increased risk (11), whereas low birth weight is protective (17). Previously reported associations with cesarean section delivery (11,15) could not be confirmed in our study. This could be due to a lack of power because, in a very large Swedish study (11), the magnitude of the increase in risk was relatively small. However, in a U.K. report, larger increases in risk were detected in a smaller study. The lack of association in our study could be explained if cesarean section itself is not the risk factor but rather some associated technique or determinant of cesarean delivery that may only be relevant in certain countries. We could not detect any association with perinatal infections recorded in the hospital notes, which agrees with a larger register study based on computerized hospital diagnosis (11). This does not exclude the possibility that infectious disease in utero or in the early neonatal period is a risk factor for diabetes because many viral diseases during pregnancy remain undiagnosed.

The most impressive increase in risk was that found for blood group incompatibility, specifically AB0 incompatibility, which had an OR of >3. This finding agrees with a previous large register-based case-control study that showed similar high ORs for blood group incompatibility syndromes, specifically with patients with a

Table 4—*ORs from a multiple logistical model including terms for cause of jaundice, treatment for jaundice, and center*

	Cases	Control subjects	OR (95% CI)	*P* value for individual variables
No jaundice	611	1,733	1.00	—
Cause of jaundice				
AB0	29	30	3.06 (1.73–5.41)	<0.001
Rh	9	16	1.39 (0.57–3.37)	0.46
Other or unknown	167	377	1.14 (0.90–1.45)	0.27
Any treatment	68	110	1.39 (0.95–2.04)	0.09

Data are *n* or ORs (95% CIs) and excludes 11 cases and 10 control subjects who had jaundice but whose treatment was unknown.

Table 5—*Logistical regression analysis of perinatal risk factors*

Variable	OR (95% CI)	*P*
Maternal age (>25 years)	1.31 (1.09–1.58)	0.004
Preeclampsia	1.49 (1.11–1.99)	0.007
Low birth weight (<2,500 g)	0.28 (0.13–0.60)	0.001
Short birth length (<50 cm)	0.74 (0.58–0.94)	0.02
Respiratory disease	1.71 (1.13–2.59)	0.01
Jaundice and		
AB0 incompatibility	3.78 (2.17–6.58)	<0.001
Rh incompatibility	1.75 (0.75–4.08)	0.19
Other or unknown cause	1.39 (1.09–1.77)	0.008

young age at diagnosis (11). The latter study was based on data prospectively recorded in the Swedish Medical Birth Registry and is free of any disease-dependent bias. In that study, it was not possible to distinguish treatment effects from diagnosis effects, but treated cases with incompatibility had higher ORs than untreated cases, and AB0 immunization seemed to be a slightly stronger risk factor than Rh immunization, although the difference was not statistically significant. Data for the present study were based on hospital records scrutinized by trained local study participants, all of whom were instructed carefully to process a similar number of patients and control subjects. This means that current data are reasonably free of disease-dependent biases. To adjust for possible differences in the sensitivity and specificity of local data sources, all analyses were stratified by center. The present analysis shows that jaundice caused either by a known cause other than blood group incompatibility or of unknown cause was associated with a slight but significant increase in risk. A possible explanation for this finding is that, because AB0 blood group incompatibility was not checked in some centers unless jaundice was severe, some incompatibilities may have been missed and the jaundice thus classified as being of unknown cause. Rh incompatibility seemed a less strong risk factor than AB0 incompatibility, although the latter was a more common finding. When analyzing treatment effect and examining the group of jaundice cases without a diagnosis of blood group incompatibility, no statistically significant effect of treatment was shown, although a tendency to have an increased OR was indicated. Logistical regression analysis indicated that blood group incompatibility was a strong independent risk factor and that phototherapy treatment per se was not associated with a statistically significant increase in risk. However, the wide 95% CIs for the OR associated with jaundice treatment in the model suggest that, as in the Swedish study (11), a possible role of phototherapy cannot be ruled out.

The mechanism by which blood group incompatibility is associated with the risk of type 1 diabetes is also unknown. One possibility is that certain risk genes in the HLA system could be connected to the severity of the disease, as proposed by one study that showed that severe Rh D immunization in pregnancy was associated with an increased frequency of HLA DQB-1 alleles (19). On the other hand, this would not explain the association with AB0 incompatibility. Because the AB0 antigens are not restricted to erythrocytes but are also found on leukocytes and other tissues, one could speculate a direct effect on the β-cells by the naturally occurring A or B antibodies. Interestingly, children dying of erythroblastosis fetalis due to severe blood group incompatibility have signs of hypoglycemia and hyperinsulinemia (20). Another possibility is that this association is related to the severe hemolysis that causes hypoxia in different organs, which connects this risk factor to the finding of neonatal respiratory disease as a risk factor.

In conclusion, the present population-based case-control study, which collected data from seven different European centers by using a common protocol, shows that several perinatal events are associated with an increased risk of type 1 diabetes. Some of the risk factors may act through nonspecific perinatal stress or may be confounded by other risk factors not yet identified. The effect of maternal-child blood group incompatibility, known to be associated with neonatal β-cell dysfunction, is so strong that a more direct effect is indicated, the mechanism of which must be further explored.

APPENDIX

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