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ORIGINAL CONTRIBUTIONS

Perinatal Factors and Development of Islet Autoimmunity in Early Childhood

The Diabetes Autoimmunity Study in the Young

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The objective of this study was to test whether maternal age at delivery, child's birth order, cesarean section, complicated delivery, maternal smoking during pregnancy, or neonatal jaundice predict islet autoimmunity in children at genetically increased risk of type 1 diabetes in a birth cohort with blood draws at ages 9, 15, and 24 months and yearly thereafter. Newborns with diabetes-associated human leukocyte antigen genotypes ($n = 938$) and offspring or siblings of persons with type 1 diabetes ($n = 428$) from the Denver, Colorado, metropolitan area were examined from January 1994 to February 2003. Information on perinatal factors was collected by using questionnaires soon after the birth. Islet autoimmunity was defined as positivity for ≥1 autoantibody to glutamic acid decarboxylase$_{65}$, insulin, or protein tyrosine phosphatase-2/ICA512 at ≥2 consecutive visits ($n = 52$; mean follow-up, 3.9 years). Complicated delivery (breech, forceps, vacuum extraction) predicted a higher risk of islet autoimmunity (hazard ratio = 2.10, 95% confidence interval: 1.09, 4.05). Increasing maternal age was related to risk of islet autoimmunity among first-degree relatives of persons with type 1 diabetes (hazard ratios = 3.96 and 8.88 for maternal ages 25–34 and ≥35 years, respectively, compared with <25 years; p for trend = 0.008. Other factors evaluated were not related to risk of islet autoimmunity. In conclusion, influences in utero or during delivery may affect the fetal immune system.

autoimmunity; child; diabetes mellitus, type I; environment; infant, newborn; perinatal care; pregnancy; prospective studies

Abbreviations: GADA, glutamic acid decarboxylase$_{65}$ autoantibodies; HLA, human leukocyte antigen; IAA, insulin autoantibodies; IA-2, protein tyrosine phosphatase-2.

Type 1 diabetes is among the most common chronic diseases with onset in childhood. The disease results from specific destruction of the insulin-producing beta cells in the pancreatic islets and is characterized by a preclinical phase of islet autoimmunity (1). The majority of cases with type 1 diabetes carry human leukocyte antigen (HLA)-*DR* and -*DQ* susceptibility genes, but these are not sufficient for development of disease. The environmental triggers of islet autoimmunity and type 1 diabetes are essentially unknown, but such factors are likely to operate early in life, maybe even in utero (2). In support for the idea that environmental factors operate in utero or early in life, some studies have found associations between specific perinatal factors and type 1 diabetes such as higher maternal age at

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delivery, delivery by cesarean section, and neonatal jaundice (3–6).

The Diabetes Autoimmunity Study in the Young (DAISY) is a prospective study that includes serial clinic visits to investigate candidate environmental risk factors for islet autoimmunity and type 1 diabetes (7, 8). Islet autoimmunity is defined by the presence of circulating glutamic acid decarboxylase$_{65}$ autoantibodies (GADA), insulin autoantibodies (IAA), and protein tyrosine phosphatase-2 (IA-2)/ICA512 autoantibodies, often referred to as islet autoantibodies. These autoantibodies are highly predictive of future development of clinical type 1 diabetes (9, 10). The objective of the present study was to investigate whether maternal age at delivery, child's birth order, cesarean section, complicated delivery, maternal smoking during pregnancy, neonatal jaundice, or phototherapy can predict the risk of developing islet autoimmunity among children at genetically increased risk of type 1 diabetes.

MATERIALS AND METHODS

Subjects and study design

From January 1994 to January 2003, more than 27,800 cord blood samples from children born at St. Joseph Hospital in Denver, Colorado, were screened for diabetes-associated HLA genotypes (7). The distribution of ethnic groups for children born at St. Joseph Hospital is similar to that of the general population of the Denver metropolitan area. We excluded families in which parents had difficulty understanding English or whose infant had a severe congenital malformation or disease. Eighty-six percent of families approached gave informed consent for genetic screening.

Samples of whole blood in ethylenediaminetetraacetic acid (EDTA) were sent to the HLA typing laboratory at Roche Molecular Systems, Inc. (Alameda, California) for polymerase chain reaction–based class II genotyping, as described previously (7). Children were categorized into three groups defined by their odds of developing type 1 diabetes by age 20 years. The high-risk genotypes (odds = 1:16) included *DRB1*04-DQB1*0302/DRB1*0301-DQB1*0201*, and the moderate-risk genotypes (odds = 1:75 for non-Hispanic Whites and 1:230 for Hispanics) were *DRB1*04-DQB1*0302/DRB1*04-DQB1*0302* or *DRB1*0301/*0301* or *DRB1*04-DQB1*0302/X* (where *X* is not *DRB1*04*, *DQB1*0302*, *DRB1*0301*, *DQB1*0602*, or *DR2* (*DRB1*15* or *16*)). All other genotypes were classified as low risk. The moderate- and low-risk HLA categories were grouped together for the present analysis. Children who had a sibling or parent with type 1 diabetes were identified from families attending clinics in the Denver metropolitan area (the majority from the Barbara Davis Center for Childhood Diabetes, Denver, Colorado) and were recruited regardless of their HLA genotype. Participants were recruited soon after birth and were scheduled for clinic visits at ages 9, 15, and 24 months and annually thereafter. Venous blood samples were collected at each clinic visit, and children who tested positive for one or more islet autoantibody were scheduled for more frequent visits.

Informed consent was obtained from parents of all children in the study, approved by the Colorado Multiple Institutional Review Board. Between January 1994 and February 2003, 1,431 children were seen in the clinic at age 15 months or earlier. The families of 1,366 children (95.5 percent) completed a mailed questionnaire about perinatal and sociodemographic factors soon after the birth of the study child (428 siblings or offspring of persons with type 1 diabetes and 938 without affected first-degree relatives).

Autoantibody assays and definition of outcome

All blood autoantibody measurements were performed in the laboratory of Dr. George Eisenbarth at the Barbara Davis Center. We used radioimmunoassays for IAA, GADA, and IA-2 autoantibodies. IAA were measured by a micro-IAA assay with a sensitivity of 58 percent, specificity of 99 percent, and interassay coefficient of variation of 11 percent (11). The combined GADA and IA-2 autoantibody radioassay was performed in duplicate on a 96-well filtration plate, and radioactivity was counted on a TopCount 96-well plate beta counter (Packard Instruments, Downers Grove, Illinois) by using a modification of a method reported previously (12). The levels of both antibodies were expressed as an index (sample counts per minute (cpm) – negative control cpm)/(positive control cpm – negative control cpm) (12). During the 1995 Immunology of Diabetes Society Workshop, the GADA assay had 82 percent sensitivity and 99 percent specificity when sera from new-onset diabetic patients aged less than 30 years were used. The interassay coefficient of variation was 6 percent. The IA-2 assay had 73 percent sensitivity and 100 percent specificity, and the interassay coefficient of variation was 10 percent (13). All samples whose IAA, GADA, or IA-2 levels exceeded the 99th percentile, and a random 10 percent of the remaining samples, were retested in a blinded manner for quality assurance purposes. The 99th percentiles based on testing 198 nondiabetic controls aged 0.4–67 years were 0.01 for IAA, 0.032 for GADA, and 0.049 for IA-2. For IA-2, the single highest value among controls, 0.07, was used as the cutoff for positivity for this assay. For GADA and IAA, the 99th percentiles were used as cutoff values for positivity.

The definition of islet autoimmunity was positivity for one or more autoantibodies at two or more consecutive clinic visits at 1–6–month intervals (of the 52 children who satisfied this definition, 16 were negative at one or more subsequent visit, whereas 14 developed clinical type 1 diabetes prior to February 28, 2003). Time of onset of islet autoimmunity was defined as the midpoint between the dates of the two clinic visits when the child was last negative and first positive for one or more autoantibodies.

Study variables

The questionnaire asked about sociodemographic and environmental factors of relevance such as the mother's education, and the child's birth order was inferred from the number of older siblings. Mothers were asked whether they smoked a total of at least 50 cigarettes when pregnant with the participating child (yes/no) and about the type of

TABLE 1. Descriptive characteristics of children in the study cohort (*n* = 1,366), Denver, Colorado, 1994–2003

	Children without siblings or parents with type 1 diabetes (*n* = 938)		Offspring or siblings of persons with type 1 diabetes (*n* = 428)	
	No.	%	No.	%
High-risk human leukocyte antigen genotype*	309	32.9	50	11.9
Ethnic group†: non-Hispanic White	617	65.8	355	82.9
Gestational diabetes mellitus‡	44	4.7	7	1.7
Maternal education§ >12 years	656	75.6	343	83.7
Gender: female	440	46.9	212	49.5
Mean age (months) at first clinic visit (standard deviation)	9.5 (0.96)		10.0 (1.92)	
Mean follow-up (months) from birth (standard deviation)¶	49.4 (31.8)		42.5 (27.5)	
Development of islet autoimmunity#	23	2.5	29	6.8
Development of type 1 diabetes**	5	0.5	9	2.1

* The high-risk genotype was *DRB1*04-DQB1*0302/DRB1*0301-DQB1*0201*. For nine siblings or offspring of persons with type 1 diabetes, data were missing.

† Based on self-report. The 394 grouped as "other" included 266 Hispanics (67.5%), 77 biracial persons (19.5%), 35 African Americans (8.9%), five Asians (1.3%), four American Indians (1.0%), five other persons (1.3%), and two persons for whom data were missing (0.5%).

‡ Excluding pregestational diabetes. Among children who were first-degree relatives of persons with type 1 diabetes, 119 (27.8%) had mothers with pregestational type 1 diabetes.

§ Maternal education when giving birth to the index child. For 77, data were missing.

¶ Time to the last clinic visit at which the child tested negative for islet autoantibodies or to the midpoint between the clinic visits at which the child was last negative and first positive.

Developed islet autoimmunity during the present follow-up: positive for one or more types of islet autoantibodies (to glutamic acid decarboxylase$_{65}$, insulin, or protein tyrosine phosphatase-2) at two or more consecutive clinic visits.

** Developed clinical type 1 diabetes subsequent to islet autoimmunity prior to February 28, 2003.

delivery—vaginal uncomplicated, vaginal complicated (e.g., breech, forceps, vacuum), or cesarean section—and whether she experienced a number of listed complications during pregnancy and delivery. The families were also asked whether the child had "yellow skin (jaundice)" or had "light therapy (phototherapy)" soon after birth. Some relatively rare complications of potential interest were not included among the main study variables because of low statistical power (see below), but they were included in regression models for controlling potential confounding.

Statistical analysis

With the cohort defined as above, and on the basis of the logistic model, we calculated that we could detect relative risks of about 2 with 80 percent power for exposures with 30–70 percent prevalence (two-sided tests, 5 percent significance level). We used Cox regression analysis to estimate hazard ratios with a 95 percent confidence interval for the relation between study variables and time to islet autoimmunity, with time from birth to development of islet autoimmunity or the last clinic visit at which the child tested negative as the main time variable (14). We evaluated family history (first-degree relative with type 1 diabetes or not), HLA risk category, ethnic group, maternal education, maternal symptoms of infections during pregnancy, maternal gestational diabetes, and the child's birth weight as potential confounders. We investigated whether the hazard ratios were of similar magnitude for children who had and did not have first-degree relatives with type 1 diabetes and for different HLA risk categories by stratified analyses and testing of the respective interactions. Unless reported otherwise, results were similar in these subgroups. We also conducted sensitivity analyses after excluding children whose mothers had type 1 diabetes because type 1 diabetes during pregnancy is associated with a number of other pregnancy complications (15). We also compared the results obtained from Cox regression analysis with those from logistic regression analysis (hazard ratios and odds ratios and their 95 percent confidence intervals) as an informal means of assessing the robustness of the results. All results were essentially the same. Outcome and exposures were defined before inspecting the relations between them. A two-sided p value of less than 0.05 or a 95 percent confidence interval excluding the value 1.00 for the hazard ratio was considered statistically significant.

RESULTS

During the most recent follow-up, 52 children had developed islet autoimmunity, of whom 14 subsequently developed clinical type 1 diabetes (table 1). Similar proportions of

TABLE 2. Associations between selected perinatal factors and development of islet autoimmunity among 1,366 children at genetically increased risk of type 1 diabetes,* Denver, Colorado, 1994–2003

	No. of person-years (n = 5,380)	No. of cases (n = 52)†	Unadjusted		Adjusted‡	
			Hazard ratio	95% CI§	Hazard ratio	95% CI
Type of delivery						
Uncomplicated vaginal¶ (n = 927)	3,675	29	1.00 (reference)		1.00	
Complicated vaginal (n = 168)	683	13	2.39	1.24, 4.60	2.10	1.09, 4.05
Cesarean section (n = 269)	1,014	10	1.22	0.59, 2.50	0.95	0.46, 1.97
Maternal age at delivery (years)#						
<25 (n = 301)	1,126	8	1.00 (reference)		1.00	
25–34 (n = 802)	3,176	29	1.29	0.59, 2.82	1.02	0.46, 2.26
≥35 (n = 254)	1,053	15	2.00	0.85, 4.72	1.71	0.71, 4.13
Test for trend			p = 0.07		p = 0.20	
Maternal smoking in pregnancy						
No (n = 1,191)	4,744	49	1.00 (reference)		1.00	
Yes (n = 163)	593	3	0.49	0.15, 1.57	0.57	0.18, 1.86
Child's birth order						
First (n = 649)	2,537	22	1.00 (reference)		1.00	
Second or higher (n = 713)	2,821	30	1.23	0.71, 2.13	1.09	0.62, 1.92
Neonatal jaundice						
No (n = 823)	3,236	33	1.00 (reference)		1.00	
Yes (n = 532)	2,098	19	0.89	0.51, 1.56	0.94	0.53, 1.67
Phototherapy						
No (n = 1,218)	4,764	47	1.00 (reference)		1.00	
Yes (n = 126)	550	4	0.75	0.27, 2.10	0.63	0.23, 1.78

* 428 siblings or offspring of persons with type 1 diabetes and 938 children with diabetes-associated human leukocyte antigen genotypes (without first-degree relatives with type 1 diabetes). Data were missing on maternal smoking in pregnancy for 12 children, birth order for four children, jaundice for 11 children, and phototherapy for 22 children.

† The number developing islet autoimmunity during the present follow-up: positive for one or more types of islet autoantibodies (to glutamic acid decarboxylase$_{65}$, insulin, or protein tyrosine phosphatase-2) at two or more consecutive clinic visits.

‡ Adjusted for having a first-degree relative with type 1 diabetes (yes/no), human leukocyte antigen risk category (*DRB1*04-DQB1*0302/DRB1*0301-DQB1*0201* or not), and ethnic group (non-Hispanic White or other).

§ CI, confidence interval.

¶ Both cesarean section and complicated vaginal delivery were compared with uncomplicated vaginal delivery. For two children, data on type of delivery were missing.

For nine children, data were missing. Test for trend was the Wald test in the model with maternal age as a continuous variable.

boys and girls were enrolled in the study (table 1), and the risk of islet autoimmunity was very similar for both, regardless of family history and ethnic group (not shown).

Maternal smoking during pregnancy, the child's birth order, neonatal jaundice, or phototherapy was not significantly related to islet autoimmunity, but there was a suggestive relation between increasing maternal age at delivery and the child's risk of islet autoimmunity that was not significant (table 2). Compared with children born as a result of an uncomplicated vaginal delivery, children who experienced a complicated delivery had an approximately twofold increased risk of later developing islet autoimmunity; being delivered by cesarean section was not related to risk of autoimmunity (table 2). These results were only marginally affected by adjustment for family history of type 1 diabetes, HLA genotype, and ethnic group (table 2). The results were also essentially unchanged after additional adjustment for maternal gestational diabetes, maternal education, maternal age at delivery, maternal symptoms of infection during pregnancy (16), and the child's birth weight (result for complicated vaginal delivery compared with uncomplicated vaginal delivery after simultaneously adjusting for all of the aforementioned factors: hazard ratio = 2.01, 95 percent confidence interval: 0.99, 4.09).

After additional stratification by having a first-degree relative with type 1 diabetes, the magnitude of the hazard ratio

TABLE 3. Type of delivery and risk of islet autoimmunity, by family history of type 1 diabetes, Denver, Colorado, 1994–2003

Type of delivery*	No. of person-years (n = 5,380)	No. of cases (n = 52)†	Unadjusted		Adjusted‡	
			Hazard ratio	95% CI§	Hazard ratio	95% CI
No first-degree relative with type 1 diabetes						
Uncomplicated vaginal (n = 685)	2,814	13	1.00 (reference)		1.00	
Complicated vaginal (n = 114)	481	6	2.66	1.01, 7.00	2.35	0.89, 6.21
Cesarean section (n = 138)	569	4	1.51	0.49, 4.63	1.46	0.48, 4.47
First-degree relative with type 1 diabetes						
Uncomplicated vaginal (n = 242)	861	16	1.00 (reference)		1.00	
Complicated vaginal (n = 54)	202	7	1.88	0.78, 4.58	2.15	0.88, 5.26
Cesarean section (n = 131)	445	6	0.71	0.28, 1.81	0.83	0.32, 2.14
Father or sibling with type 1 diabetes¶						
Uncomplicated vaginal (n = 211)	751	14	1.00 (reference)		1.00	
Complicated vaginal (n = 40)	141	5	1.90	0.68, 5.24	1.95	0.70, 5.43
Cesarean section (n = 57)	202	6	1.54	0.59, 4.01	1.60	0.61, 4.17

* Likelihood ratio test for interaction between type of delivery and family history of type 1 diabetes; $p = 0.58$. Both cesarean section and complicated vaginal delivery were compared with uncomplicated vaginal delivery. For two children, data on type of delivery were missing.

† Number developing islet autoimmunity during the present follow-up: positive for one or more types of islet autoantibodies (to glutamic acid decarboxylase$_{65}$, insulin, or protein tyrosine phosphatase-2) at two or more consecutive clinic visits.

‡ Adjusted for human leukocyte antigen risk category (*DRB1*04-DQB1*0302/DRB1*0301-DQB1*0201* or not) and ethnic group (non-Hispanic White or other).

§ CI, confidence interval.

¶ Excluding children whose mothers had type 1 diabetes.

for complicated delivery was also similar (table 3). In spite of a relatively low number of children in each category, this result was also similar after excluding those whose mothers had type 1 diabetes (table 3).

When we studied specific complications during pregnancy or delivery potentially associated with a complicated delivery in the whole study cohort, only premature rupture of membranes and prolonged labor seemed to be more common in complicated vaginal deliveries compared with other types of deliveries (table 4). Of the 13 cases who experienced a complicated vaginal delivery and then developed islet autoimmunity during follow-up, the mothers of three experienced prolonged labor (23.1 percent), and the mother of one experienced premature rupture of membranes (not shown). After simultaneous adjustment for family history of type 1 diabetes, ethnic group, HLA risk category, maternal preeclampsia or toxemia, premature rupture of membranes, and prolonged labor, the hazard ratio for a complicated vaginal

TABLE 4. Specific complications during pregnancy or delivery potentially associated with a complicated pregnancy in the whole study cohort,* Denver, Colorado, 1994–2003

	Uncomplicated vaginal delivery (n = 927)		Complicated vaginal delivery (n = 168)		Cesarean section (n = 269)	
	No.	%	No.	%	No.	%
High blood pressure	130	11.2	16	9.6	70	26.2
Preeclampsia or toxemia	41	4.5	9	5.4	44	16.7
Premature labor	157	17.1	28	16.9	54	20.3
Premature rupture of membranes	32	3.5	13	7.9	12	4.5
Prolonged labor	43	4.7	28	17.0	31	11.7

* For some, data on pregnancy complications were missing. Percentages are for those children for whom data were valid. For only one to two children experiencing complicated vaginal deliveries, the mother had an insufficient cervix, placenta previa, or abruptio placenta.

TABLE 5. Maternal age at delivery and islet autoimmunity, by family history of type 1 diabetes, Denver, Colorado, 1994–2003

Maternal age (years) at delivery*	No. of person-years (*n* = 5,380)	No. of cases† (*n* = 52)	Unadjusted		Adjusted‡	
			Hazard ratio	95% CI§	Hazard ratio	95% CI
No first-degree relative with type 1 diabetes						
<25 (*n* = 253)	944	7	1.00 (reference)		1.00	
25–34 (*n* = 528)	2,226	11	0.68	0.26, 1.75	0.55	0.21, 1.46
≥35 (*n* = 149)	674	5	0.99	0.31, 3.13	0.84	0.26, 2.69
Test for trend			*p* = 0.81		*p* = 0.59	
First-degree relative with type 1 diabetes						
<25 (*n* = 48)	182	1	1.00 (reference)		1.00	
25–34 (*n* = 274)	950	18	3.41	0.45, 25.5	3.96	0.53, 29.9
≥35 (*n* = 105)	378	10	4.79	0.61, 37.4	8.88	1.11, 71.4
Test for trend			*p* = 0.07		*p* = 0.008	
Father or sibling with type 1 diabetes¶						
<25 (*n* = 37)		1	1.00 (reference)		1.00	
25–34 (*n* = 190)		15	3.11	0.41, 23.5	3.77	0.50, 28.7
≥35 (*n*= 82)		9	4.11	0.52, 32.5	9.62	1.17, 78.9
Test for trend			*p* = 0.09		*p* = 0.007	

* Test for interaction between maternal age (continuous variable) and family history of type 1 diabetes; $p = 0.15$. Test for trend was the Wald test in the model with maternal age as a continuous variable.

† Number developing islet autoimmunity during the present follow-up: positive for one or more types of islet autoantibodies (to glutamic acid decarboxylase$_{65}$, insulin, or protein tyrosine phosphatase-2) at two or more consecutive clinic visits.

‡ Adjusted for human leukocyte antigen risk category (*DRB1*04-DQB1*0302/DRB1*0301-DQB1*0201* or not) and ethnic group (non-Hispanic White or other).

§ CI, confidence interval.

¶ Excluding children whose mothers had type 1 diabetes.

versus an uncomplicated vaginal delivery was 2.24 (95 percent confidence interval: 1.13, 4.43). The hazard ratio for cesarean section was 0.89 (95 percent confidence interval: 0.52, 1.91).

After stratification by family history, we found that increasing maternal age at delivery predicted a higher risk of islet autoimmunity among those with a family history of type 1 diabetes, while there was no clear relation among children who did not have first-degree relatives with type 1 diabetes (table 5). The number of cases with islet autoimmunity did not allow a meaningful analysis after stratification by whether the children had a sibling, mother, or father with type 1 diabetes. However, we also conducted the same analysis after excluding children whose mothers had type 1 diabetes to exclude possible confounding (lower part of table 5). In spite of a relatively low number of children in each category, the results were also similar after this exclusion. The interaction between maternal age (as a continuous variable) and type 1 diabetes in first-degree relatives was not statistically significant ($p = 0.15$).

DISCUSSION

The present study is the first known to demonstrate that a complicated delivery is related to a higher risk of subsequent development of islet autoimmunity in children. We also found a suggestive relation between increased maternal age at delivery and increased risk of autoimmunity among siblings or offspring of persons with type 1 diabetes. These observations indicate the importance of pre- or perinatal events as triggers of islet autoimmunity in some cases.

Our study investigated "prediabetic" islet autoimmunity as the outcome by using a prospective design. Previous case-control studies have found various indicators of complications during pregnancy and delivery, such as preeclampsia, cesarean section, and feto-maternal blood group incompatibility, to be associated with increased risk of clinical type 1 diabetes, although results have not been entirely consistent (3, 5, 17, 18). Complications during pregnancy have also been related to increased risk of atopic disorders (19). Together with these findings, our observations suggest that some pregnancy complications may affect the fetal immune system with medium- to long-term consequences, although the mechanisms are not known. Maternal diabetes, either pregestational or gestational, is associated with an increased risk of a number of pregnancy complications and was probably one of the most important potential confounders in the present study. However, the results persisted even after adjusting for gestational diabetes and excluding children

whose mothers had type 1 diabetes, demonstrating that maternal diabetes could not explain our findings.

One way of elucidating the potential mechanisms is to investigate whether more-specific types of complications are responsible for the observed association. A large number of conditions are related to breech deliveries, vacuum extraction, and forceps deliveries. Most breech deliveries are performed by cesarean section, so it is likely that forceps and vacuum extraction are most relevant in our context. Many different conditions and causes can lead to such deliveries, some unknown, and it is likely that each single type of complication would have been too rare for a meaningful analysis in the present cohort. The higher risk of islet autoimmunity among those experiencing a complicated vaginal delivery persisted even after we adjusted for several specific complications, indicating that none of the specific factors studied could explain the association with complicated delivery. This finding suggests that other specific types of complications may be involved, low statistical power may be an issue, or several different types of complications may contribute to an increased risk of islet autoimmunity, perhaps through diverse mechanisms.

In some case-control studies, delivery by cesarean section has been associated with a slightly increased risk of type 1 diabetes (3, 17), although other large studies have not found any association (5, 18, 20), consistent with the present study of islet autoimmunity. Indications for cesarean section may differ between geographic regions and may have changed over time, thus making interpretation of these studies difficult.

Associations of birth order with risk of type 1 diabetes have been particularly inconsistent in previous studies (4–6, 17, 18, 21, 22). On the other hand, a relation between increased maternal age at delivery and increased risk of type 1 diabetes in children has been a relatively consistent finding, although the potential mechanisms explaining this relation remain elusive (3–6, 17, 22).

To our knowledge, the present study is the first to demonstrate that this relation may also exist for islet autoimmunity. However, this relation was found among only those children who had parents or siblings with type 1 diabetes. This finding should be interpreted with some caution because the interaction between family history of type 1 diabetes and maternal age at delivery was not statistically significant. A previous study did not find a significant relation between maternal age at delivery and islet autoimmunity among children of diabetic parents (23). One study has suggested that among offspring of mothers with type 1 diabetes, the relation between maternal age at delivery and risk of type 1 diabetes in the children is inverse (24), although this finding was not supported by a population-based Finnish study (21). In previous studies (3), jaundice at birth or soon after birth has been shown to be associated with increased risk of type 1 diabetes, and it has been suggested that this association is due to the phototherapy that these children receive (25). However, this finding was not supported by our study of islet autoimmunity. A reduced risk of type 1 diabetes among children whose mothers smoked during pregnancy was first suggested by Dahlquist and Källén (3), which has not been conclusively supported by other studies (22, 23) and was not supported by the present study.

Strengths and limitations of the present study

Strengths of the current study include that it is prospective, with serial follow-up and assessment of exposure before development of outcome. The fact that maternal complications during pregnancy and delivery were self-reported after the birth of the child is a potential limitation, but most of the factors studied are relatively easily recalled; potential misclassification is unlikely to be related to the outcome of this study. Any potential misclassification of exposure factors is therefore likely to attenuate the estimated relations (26). Although we adjusted for a number of factors in the analyses, we cannot rule out the possibility of unknown confounding factors. Our study has shown that a complicated delivery is related to islet autoimmunity, a state that nearly all children who develop type 1 diabetes go through, but the results do not automatically relate to type 1 diabetes. Because the cohort consists of children selected to be at genetically increased risk of type 1 diabetes, the results are not necessarily directly applicable to the general population. However, because the majority of children developing type 1 diabetes have a genetically increased risk, the present results are likely to be of relevance at the population level.

Conclusion

Our study found that a complicated delivery predicted an increased risk of islet autoimmunity early in life and that increased maternal age at delivery predicted increased risk among those who had first-degree relatives with type 1 diabetes. These findings suggest that influences in utero or during delivery may affect the fetal immune system, with long-term consequences. Future studies with a larger number of cases with islet autoimmunity should investigate the role of specific types of complications during pregnancy and delivery.

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