

Previous Maternal Abortion, Longer Gestation, and Younger Maternal Age Decrease the Risk of Type 1 Diabetes Among Male Offspring

IBEN BACHE, MD
TROELS BOCK, MD

AAGE VØLUND, PHD
KARSTEN BUSCHARD, MD

OBJECTIVE — To identify possible influences and interactions of perinatal determinants in the subsequent development of type 1 diabetes.

RESEARCH DESIGN AND METHODS — The data were obtained from children born in Denmark during the periods 1978–1982 and 1984–1986 and admitted to a Danish hospital with newly diagnosed type 1 diabetes between 1978 and 1995; 857 patients fulfilled the criteria. The study was conducted by combining and analyzing two national registries: the National Patient Registry and the Medical Birth Registry. For each diabetic child, two control children were randomly selected, matched by sex, time, and district of delivery.

RESULTS — By multivariate logistic regression analysis, the following significant determinants were identified. Male offspring showed decreased risk when born of mothers who had had one or more abortions (odds ratio [OR] 0.66 [95% CI 0.48–0.92]) and with long duration of gestation (linearly with OR 0.91 per week [0.85–0.99]), while increased risk was found for high maternal age (linearly with OR 1.03 per year [1.00–1.06]). Female offspring showed no such association. No significant differences between diabetic patients and control subjects were found with respect to paternal age, maternal parity, placental weight or any of the birth size parameters, or interventions and complications during delivery.

CONCLUSIONS — The findings show that perinatal determinants may influence the risk of subsequent development of type 1 diabetes in a sex-specific manner.

Diabetes Care 22:1063–1065, 1999

Type 1 (insulin-dependent) diabetes is a chronic autoimmune disease with selective destruction of the insulin-producing β -cells. Both genetic susceptibility and environmental factors are believed to be of importance (1). Since type 1 diabetes can develop in early childhood, it is natural to consider intrauterine life and perinatal exposure (2) as factors involved in the pathoetiology. Accordingly, a number of studies have examined the possible relationship between perinatal

events and risk of developing type 1 diabetes and have found high maternal age to be a significant factor (3–7). However, the findings concerning the effects of birth order, preterm birth, birth weight, and complications during delivery are contradictory (3–11).

This article presents the results of an analysis of the possible influences and interactions of a number of perinatal determinants in subsequent development of type 1 diabetes. Two of the parameters, number of

previous maternal abortions and placental weight, have not been examined before. The investigation is a Danish nationwide case-control study based on registry data.

RESEARCH DESIGN AND

METHODS — The National Patient Registry in Denmark stores data for all admissions to Danish hospitals. According to epidemiological studies, >99% of children with type 1 diabetes are treated in a department of pediatric or internal medicine in Denmark (12). In the period 1978–1995 (inclusive), 857 children born between 1978–1982 and 1984–1986 (inclusive) were recorded with a diagnosis of diabetes (according to the *International Classification of Diseases, 10th Revision*) (13).

The Danish Medical Birth Registry (MBR) contains data on pregnancy and delivery for >99% of all infants born in Denmark since 1973 (14). The data are based on reports by midwives at the time of birth. The parameter placental weight was not available for infants born in 1983; thus, this population was excluded from the analysis. The unique 10-digit personal identification number given to everyone living in Denmark allowed linkage between the two registries. For each diabetic child, two control subjects were randomly selected from among all newborns delivered in the same month, of the same sex, and within the same district. Twin individuals (18 patients and 27 control subjects) were excluded, giving 839 patients and 1,687 control subjects.

The following variables recorded in the MBR at the time of birth were analyzed for patients and control subjects: maternal and paternal age at delivery, number of pregnancies, maternal parity, gestational age, birth weight and length, placental weight, and interventions and complications before and during delivery. Number of abortions was calculated by subtracting maternal parity from number of pregnancies; thus, the parameter includes both induced and spontaneous abortions. In addition, ponderal index (weight [grams] \times 100/length³

From the Bartholin Institutttet (I.B., T.B., K.B.), Kommunehospitalet; and Statistics Diabetes Haematology (A.V.), Novo Nordisk, Copenhagen, Denmark.

Address correspondence and reprint requests to Iben Bache, MD, Bartholin Institutttet, Kommunehospitalet, DK-1399 Copenhagen K, Denmark. E-mail: buschard@post6.tele.dk.

Received for publication 30 November 1998 and accepted in revised form 18 March 1999.

Abbreviations: MBR, Medical Birth Registry; OR, odds ratio.

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

Table 1—Multivariate ORs for perinatal risk factors in diabetic patients and control subjects

	Male subjects	Female subjects	Male + female subjects
<i>n</i>	1,075	1,024	2,099
Abortion			
0	1	1	1
1	0.65 (0.47–0.90)	0.90 (0.65–1.24)	0.76 (0.60–0.95)
≥2	0.53 (0.30–0.92)	0.81 (0.46–1.44)	0.65 (0.44–0.97)
<i>P</i> *	0.004	0.66	0.01
Gestational age (per week)	0.91 (0.84–0.98)	0.96 (0.89–1.03)	0.93 (0.89–0.98)
<i>P</i> *	0.02	0.21	0.01
Maternal age (per year)	1.03 (1.00–1.06)	1.02 (0.99–1.05)	1.03 (1.01–1.04)
<i>P</i> *	0.04	0.13	0.01
<i>P</i> †	0.006	0.37	0.0004

Data are ORs, (95% CI). For abortions, 0 is the reference group. *Significance of the contribution of each variable adjusted for the effects of the others; †significance of all three explanatory variables.

[cubic centimeters]) was calculated and analyzed. The relative deviation in birth weight was calculated relative to gestational age as described in STATISTICAL ANALYSES. Completeness of the parameters in our study was 66% for paternal age, 83% for gestational age, 99.9% for birth weight and length, and 88% for placental weight. Registration of maternal age, parity, and number of pregnancies was complete. No difference in the level of completeness was found between the diabetic and control groups.

The study was approved by the Danish Scientific-Ethical Committee and the Danish Data Protection Agency.

Statistical analyses

Univariate and multivariate logistic regression was used to estimate the odds ratio (OR), with a 95% CI, and *P* value for the significance of the explanatory variable. The relationship between the logarithm of the birth weight and gestational age in the control material was described as a quadratic polynomial. Separate analyses were carried out for male and female subjects. For all children, the relative deviation in birth weight was calculated as the difference between the logarithm of observed weight and that for expected weight, according to the quadratic polynomials divided by the residual standard deviation for the control material.

Variables were analyzed simultaneously and included in the multivariate model by stepwise forward selection of the most significant. The significance of all the selected variables was confirmed by backward elimination. The multivariate logistic regression analysis was based on 695 patients and 1,404 control subjects with complete data. A 5% significance level was

used for the analyses. The statistical computations were performed on a DECpcXL590 computer using APL software validated relative to the SAS procedures LOGISTIC and GLM.

RESULTS — Among mothers of the diabetic patients, 76.0% had had no abortion, 19.0% one abortion, and 5.0% two or more abortions, while among mothers of the control subjects, 70.6% had had no abortion, 22.6% one abortion, and 6.7% two or more abortions. Gestational age was 39.5 ± 1.8 (SD) weeks for the children who later developed diabetes and 39.7 ± 1.7 weeks for the control subjects. Maternal age was, on average, 27.0 ± 4.8 years for patients and 26.5 ± 4.7 years for control subjects.

All data were subjected to multivariate logistic regression analysis and adjusted ORs were calculated (Table 1). The OR for sons born of mothers who had had one abortion was 0.66, and of those with two or more abortions, 0.53. Regarding the week of gestation, the adjusted log relative risk was found to decrease linearly with length of gestation for male offspring by 0.91 per week. Maternal age showed a linear increase in log relative risk of 1.03 with each year of increased age only for male offspring, while for females, none of the factors were significantly associated with diabetes. With respect to paternal age, maternal parity, placental weight, birth weight, birth length, ponderal index, and relative deviation in birth weight, no significant multivariate differences of case-control status were found, either in the overall or in sex-specific analysis.

Among the interventions studied, the use of an oxytocic drug was found to differ significantly (OR 1.30 [1.03–1.65]), though

not in any of the sex-specific analyses. No significant differences were found concerning the effect of medical induction, puncture, or rupture of the fetal membrane, episiotomy, breech or vacuum extraction, or cesarean. Among the delivery complications observed, there was a significant difference with respect to placenta previa in the overall analysis (four diabetic patients and none among control subjects, *P* = 0.02) but not in any of the sex-specific analyses, while retained placenta, placenta abruptio, hydramnios, preeclampsia, fetal asphyxia, and maternal disease were not found to differ significantly in any of the analyses.

CONCLUSIONS — Number of abortions, gestational age and maternal age were all found to be independently associated with type 1 diabetes, but only for males. The results were based on multivariate logistic regression analysis, which allows independent assessment of the effect of each factor.

The present epidemiological study took advantage of the effective population-based registries based on the Danish public health care system. The data used were collected routinely at birth, a considerable time before disease manifestation, and were, therefore, not likely to be biased. The precision of the parameters in the MBR has previously been investigated for preterm deliveries (15). Regarding, for example, gestational age, the concordance between the MBR and the medical records was found to be 87% when agreement was defined as within 1 week. The precision is similar for diabetic patients and control subjects and, therefore, only leads to unity of the OR.

The finding that abortion is a protective factor for childhood diabetes in subsequent offspring is a new observation, which may give rise to future studies. It is unknown whether induced and spontaneous abortions are of equal importance. Regarding the latter, hypothetically, one explanation could be that the risk of spontaneous abortion and the risk of type 1 diabetes among later offspring have a common source. Women who have an abortion have a lower level of estrogen and a higher percentage of free testosterone early in pregnancy (16,17). In nonobese diabetic mice, neonatal treatment with testosterone was found to decrease the incidence of diabetes, while endogenous estrogen contributed to the disease process (18). It may be speculated that women with a decreased level of the estrogen-to-testosterone ratio during early pregnancy have on the one hand an increased risk of abortion, and on the other a decreased risk of type 1 diabetes in male offspring. The comparatively higher diabetes risk for male offspring of mothers with no previous abortion may give rise to speculations regarding a possible generally increased estrogen exposure, which has been discussed for other diseases (19).

This study showed that the risk of type 1 diabetes decreased linearly with increased duration of gestation, but this was only significant for male newborns. This finding seems to be new, insofar as it was due to a general effect and not especially to certain subgroups, e.g., extremely preterm children. In order to assess the impact of gestational age, we have studied birth size carefully. We found no differences between the diabetic and control groups in any of the birth-size parameters: weight, length, or ponderal index. The effect of interaction of birth weight and gestational age was studied by calculating standardized birth weight according to gestational age, and no differences between diabetic patients and control subjects were found. Length of gestation <38 weeks has previously been studied as a possible risk factor: one study found a higher risk of developing type 1 diabetes (5), but this was not found in other studies (4,6,7). An increased risk of diabetes for children with heavy birth weight has been reported once (8), while a number of studies have found no such association (4,6,9,10). One study found an increased risk for children who were heavy for their gestational date (defined as >2 SDs from the expected weight according to gestational age) (11).

Increased maternal age as a risk factor of diabetes development is consistent with earlier studies (3–7), but the linear trend and its assignment to male offspring has not been described before.

Interventions and complications during delivery were examined as possible indicators of intrauterine and perinatal disturbances. Oxytocic infusion was found to be an independent risk factor, but only when the two sexes were analyzed together. One study has previously looked at the use of oxytocic infusion, and it found no association with type 1 diabetes (7).

Maternal type 1 diabetes is a well-known risk factor for childhood diabetes. In a Danish study, prevalence of maternal type 1 diabetes among diabetic children was found to be 2.0–2.5% (9). Theoretically, maternal diabetes is included, among other diseases, in the parameter “maternal disease.” The precise numbers of patients in the two groups are unknown, but are expected to be as low as indicated by the percentage mentioned and, therefore, unlikely to distort the findings decisively.

In conclusion, we found an increased risk of type 1 diabetes in male offspring of mothers with no previous abortions, short gestation, and high maternal age. Since this association was not seen for female offspring, the study suggests that perinatal determinants influence the risk of subsequent development of type 1 diabetes in a sex-dependent manner.

Acknowledgments — This work was supported by Sigrig Rigmor Morans Mindelegat.

References

- Atkinson MA, Maglaren NK: The pathogenesis of insulin-dependent diabetes mellitus. *N Engl J Med* 24:1428–1436, 1994
- Buschard K, Jørgensen M, Aaen K, Bock T, Josefsen K: Prevention of diabetes mellitus in BB rats by neonatal stimulation of beta cells. *Lancet* 335:134–135, 1990
- Flood TM, Brink SJ, Gleason RE: Increased incidence of type 1 diabetes in children of older mothers. *Diabetes Care* 5:571–573, 1982
- Blom L, Dahlquist G, Nyström L, Sandström A, Wall S: The Swedish childhood diabetes study: social and perinatal determinants for diabetes in childhood. *Diabetologia* 32:7–13, 1989
- Dahlquist G, Källén B: Maternal-child blood group incompatibility and other perinatal events increase the risk for early-onset type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 35:671–675, 1992

- Patterson CC, Carson DJ, Hadden DR, Waugh NR, Cole SK: A case-control investigation of perinatal risk factors for childhood IDDM in Northern Ireland and Scotland. *Diabetes Care* 17:376–381, 1994
- McKinney PA, Parslow R, Gurney K, Law G, Bodansky HJ, Williams DRR: Antenatal risk factors for childhood diabetes mellitus: a case-control study of medical record data in Yorkshire, UK. *Diabetologia* 40:933–939, 1997
- Metcalfe MA, Baum JD: Family characteristics and insulin dependent diabetes. *Arch Dis Child* 67:731–736, 1992
- Bock T, Pedersen CR, Volund AA, Pallesen CS, Buschard K: Perinatal determinants among children who later develop IDDM. *Diabetes Care* 17:1154–1157, 1994
- Lawler-Heavner J, Cruickshanks KJ, Hay WW, Gay EC, Hamman RF: Birth size and risk of insulin-dependent diabetes mellitus (IDDM). *Diabetes Res Clin Pract* 24:153–159, 1994
- Dahlquist G, Bennich SS, Källén B: Intrauterine growth pattern and risk of childhood onset insulin dependent (type 1) diabetes: population based case-control study. *BMJ* 313:1174–1177, 1996
- Christau B, Kromann H, Andersen OO, Christy M, Buschard K, Arnung K, Kristensen IH, Peitersen B, Steinrud J, Nerup J: Incidence, seasonal and geographical patterns of juvenile-onset insulin-dependent diabetes mellitus in Denmark. *Diabetologia* 13:281–284, 1977
- World Health Organization: *ICD-10: International Statistical Classification of Diseases and Related Health Problems*. 10th rev. Geneva, World Health Org., 1992
- Knudsen LB: *Social risk factors for low birth-weight and infant mortality in Denmark 1982–1983*. Danish Department of Health, Copenhagen, Vitalstatistik, 1988
- Kristensen J, Langhoff-Roos J, Skovgaard LT, Kristensen FB: Validation of the Danish Birth Registration. *J Clin Epidemiol* 49: 893–897, 1996
- Takeuchi T, Nishii O, Okamura T, Yaginuma T, Kawana T: Free testosterone and abortion in early pregnancy. *Int J Gynecol Obstet* 43:151–156, 1993
- Aksoy S, Celikkanat H, Senöz S, Gökmen O: The prognostic value of serum estradiol, progesterone, testosterone and free testosterone levels in detecting early abortions. *Eur J Obstet Gyn R B* 67:5–8, 1996
- Hawkins T, Gala RR, Dunbar JC: The effect of neonatal sex hormone manipulation on the incidence of diabetes in nonobese diabetic mice. *Proc Soc Exp Biol Med* 202: 201–205, 1993
- Sharpe RM, Skakkebaek NE: Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* 341:1392–1395, 1993