Maternal and paternal age at delivery, birth order, and risk of childhood onset type 1 diabetes: population based cohort study

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Abstract

Objective To estimate the associations of maternal and paternal age at delivery and of birth order with the risk of childhood onset type 1 diabetes.

Design Cohort study by record linkage of the medical birth registry and the national childhood diabetes registry in Norway.

Setting Norway.

Subjects All live births in Norway between 1974 and 1998 (1.4 million people) were followed for a maximum of 15 years, contributing 8.2 million person years of observation during 1989-98. 1824 cases of type 1 diabetes diagnosed between 1989 and 1998 were identified.

Main outcome measures Incidence of type 1 diabetes.

Results There was no association between maternal age at delivery and type 1 diabetes among firstborn children, but among fourthborn children there was a 43.2% increase in incidence of diabetes for each five year increase in maternal age (95% confidence interval 6.4% to 92.6%). Each increase in birth order was associated with a 17.9% reduction in incidence (3.2% to 30.4%) when maternal age was 20-24 years, but the association was weaker when maternal age was 30 years or more. Paternal age was not associated with type 1 diabetes after maternal age was adjusted for.

Conclusions Intrauterine factors and early life environment may influence the risk of type 1 diabetes. The relation of maternal age and birth order to risk of type 1 diabetes is complex.

Introduction

Several studies have investigated the relation between maternal age at delivery or birth order and risk of childhood onset type 1 diabetes.[1–12] Many of these studies were relatively small, used census data as controls or siblings as controls, and inappropriately analysed the data as if they arose from a cohort study.[1 2 6 12 13] Some studies found a weak increase in risk of type 1 diabetes in children born to older mothers, although others found no significant association. Studies of birth order have given particularly inconsistent results. Results from studies of association between paternal age at delivery and risk of type 1 diabetes have also been inconsistent.[4 6 7 11]

The objective of this study was to estimate the associations of maternal and paternal age at delivery and of birth order with the incidence of type 1 diabetes and the interactions between these variables.

Subjects and methods

In Norway, all newly diagnosed cases of type 1 diabetes in children under 15 years old have been prospectively registered in the national childhood diabetes registry since 1 January 1989.[14] We designed a cohort study linking records in the medical birth registry with those in the national childhood diabetes registry through the unique personal identification number assigned to all residents of Norway. The study was approved by the regional ethics committee and the National Data Inspectorate.

All live births in Norway between 1974 and 1998 contributed time under observation from birth to diagnosis of type 1 diabetes (from 1989 to 1998), age 15 years, death in the first year of life, or 31 December 1998, whichever occurred first. The child's birth order was inferred from the number of previous births (including stillbirths) reported by the mother at the time of birth of the index child.

We calculated incidence as the number of incident cases divided by the person years under observation in each category using Datab in the Epicure package, version 1.8w.[15] We estimated rate ratios with 95% confidence intervals by Poisson regression analyses.

We included calendar period of birth in five year categories and age group in three year categories to adjust for possible period effects. To assess whether the associations of parental age and birth order with type 1 diabetes were the same for different levels of other exposures, age groups, sex, and calendar periods, we inspected the results of stratified analyses and tested the significance of the respective interaction terms.

Results

A total of 1 382 602 individuals contributed 8 166 731 person years under observation between 1989 and 1998. The mean time from birth to censoring or type 1 diabetes was 10.2 (SD = 5.0) years, and the mean time under observation after 1 January 1989 was 5.9 (3.3) years. The mean age at diagnosis among the 1824 who developed type 1 diabetes was 8.6 (3.7) years.

We found a weak crude association between maternal age at delivery and incidence of type 1 diabetes (table). There were no significant crude associations between birth order and incidence of type 1 diabetes (table). However, after stratification, an interaction between maternal age at delivery and birth order appeared.

We found no association between maternal age at delivery and incidence of type 1 diabetes among firstborn children, but among second or later born children there was a positive association. The strength of the association increased with birth order (figure). For instance, among fourthborn children each five year

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Maternal and paternal age at delivery, birth order, and rate ratio of childhood onset type 1 diabetes

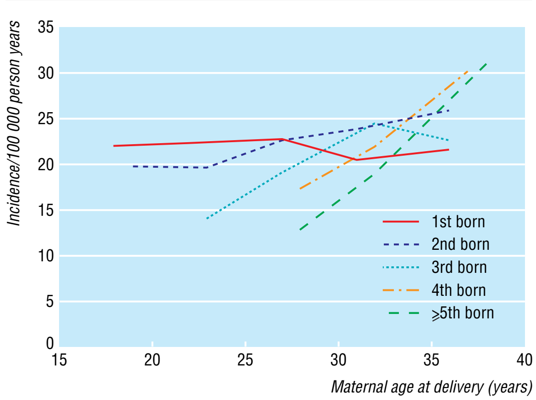
	No with diabetes	Person years	Rate ratio (95% CI) Unadjusted	Adjusted*
Maternal age (years)				
<20	99	451 574	1.0	1.0
20-24	468	2 219 415	0.96 (0.77 to 1.20)	1.00 (0.80 to 1.24)
25-29	659	2 982 226	1.01 (0.82 to 1.25)	1.09 (0.88 to 1.35)
30-34	414	1 788 072	1.06 (0.85 to 1.32)	1.18 (0.94 to 1.46)
⩾35	172	672 566	1.17 (0.91 to 1.49)	1.34 (1.04 to 1.71)
Test for trend			P=0.06	P<0.001
Birth order				
1st	772	3 457 974	1.0	1.0
2nd	648	2 886 296	1.01 (0.91 to 1.12)	1.01 (0.91 to 1.12)
3rd	279	1 291 460	0.97 (0.84 to 1.11)	0.98 (0.85 to 1.12)
4th	79	340 145	1.04 (0.83 to 1.31)	1.05 (0.83 to 1.32)
⩾5th	34	137 978	1.10 (0.78 to 1.56)	1.10 (0.78 to 1.55)
Test for trend			P=0.78	P=0.70
Paternal age (years)				
<25	298	1 318 112	1.0	1.0
25-29	572	2 696 972	0.94 (0.82 to 1.08)	0.96 (0.83 to 1.10)
30-34	517	2 167 845	1.06 (0.91 to 1.22)	1.11 (0.96 to 1.28)
35-39	221	953 271	1.03 (0.86 to 1.22)	1.11 (0.93 to 1.32)
⩾40	98	410 621	1.06 (0.84 to 1.33)	1.16 (0.92 to 1.46)
Test for trend			P=0.33	P=0.02

*Adjusted for age group and year of birth.

increase in maternal age was associated with a 43.2% increase (95% confidence interval 6.4% to 92.6%) in incidence of type 1 diabetes.

Compared with firstborn children, the incidence of type 1 diabetes was lower for second or later children when maternal age was low (figure). For instance, among children born to mothers aged 20-24 years at delivery, each increase in birth order was associated with a 17.9% reduction in the incidence of type 1 diabetes (3.2% to 30.4%). The association was weaker or non-existent when maternal age at delivery was 30 years or more (see *BMJ*'s website for more details).

There was a weak association between incidence of type 1 diabetes and paternal age at delivery. After the effects of maternal age and birth order were adjusted for, there was no significant association between paternal age and type 1 diabetes. The effects of maternal age



Maternal age at delivery and incidence of childhood onset type 1 diabetes by birth order. Data points are crude incidences in the maternal age groups <20, 20-24, 25-29, 30-34, and ⩾35 years, with the points placed at the mean maternal age within each category. There were no diabetic people with certain rare combinations of maternal age and birth order (birth order ⩾3 with maternal age <20 and birth order ⩾4 with maternal age <25)

and birth order, however, were essentially unchanged after adjustment for paternal age. All results were essentially unchanged after adjustment for maternal diabetes, pre-eclampsia, haemorrhage during pregnancy, caesarean delivery, sex, and birth weight.[16]

Discussion

We found that the association between maternal age and childhood onset type 1 diabetes increased with rising birth order. Furthermore, any association between paternal age and type 1 diabetes was secondary to maternal age at delivery. The advantages of this study were the large sample size and the fact that the data were based on computerised registries with nearly complete coverage. We cannot, however, exclude confounding by unmeasured factors such as socioeconomic status of the children's families, maternal smoking during pregnancy, or whether delayed or early childbearing and number of births were intentional.

Other studies

A previous study which tested for an interaction between maternal age and birth order found no significant interaction.[12] One problem with this study was that the authors used cohort analysis of data arising from a case-control study with siblings as controls.[12] This probably biased their results.[13] Furthermore, results from families with type 1 diabetes cannot readily be generalised to the total population. On the other hand, we cannot exclude the possibility that the effects of maternal age and birth order on risk of type 1 diabetes are different in different populations.

Several studies have found a significant crude association between increased maternal age and increased risk of type 1 diabetes.[1-4 6 9 10 12] Some of these studies used national reference data as controls[1] or used siblings as controls.[2 12] In some studies, the association was reported to disappear after birth order or other potential confounders were adjusted for.[6 17] Other studies, often with relatively small sample sizes, did not find any significant crude association between maternal age at delivery and type 1 diabetes.[8]

Birth order and paternal age

Associations of birth order and paternal age with risk of type 1 diabetes have been particularly inconsistent in previous studies. Both significantly higher risk[4 6] and lower risk[10] among firstborn children compared with second or later born children have been found, and there was evidence of heterogeneity between centres in two of these studies.[4 10] Some studies have not found any significant association between birth order and type 1 diabetes.[8 9 11] Paternal age at delivery has been negatively associated[6] and positively associated with risk of type 1 diabetes.[4] One study found a U shaped relation,[7] but others found no significant association.[11] Our results indicate that these inconsistencies may be due to small sample sizes, no adjustment for relevant confounders, and lack of stratification by maternal age and birth order.

Possible explanations for the effect

Maternal age and parity are associated with various sociodemographic and biological factors. Delayed childbearing is associated with longer maternal educa-

What is already known on this topic

Maternal age at birth is positively associated with risk of childhood onset type 1 diabetes

Studies of the effect of birth order on risk of type 1 diabetes have given inconsistent results

What does this study add?

In a national cohort, risk of diabetes in firstborn children was not associated with maternal age

Increasing maternal age was a risk factor in children born second or later

The strength of the association increased with increasing birth order

tion, complications in pregnancy, lower birth weight, fetal loss, and perinatal mortality.[18 19] Some of these associations depend on maternal parity.[18] Parous women who give birth at older ages may have had short or long intervals between previous pregnancies and may have had varying number of previous abortions or stillbirths.[19] Increasing age of the mother may be a marker for accumulated exposures such as infections or environmental toxins. Fetomaternal immune responses may also change with each pregnancy,[20] and this could partly explain our results.

Maternal age and birth order are also likely to influence a child's environment in early life. For instance, feeding practices, neonatal care, and exposure to infections may differ depending on the age of the mother and the number of siblings. McKinney et al have found some evidence that early attendance at daycare centres, as a measure of childhood infections, is associated with lower risk of type 1 diabetes.[21] However, conflicting evidence from other studies exists.[22] In conclusion, our findings indicate that the relation between maternal age, birth order, and risk of type 1 diabetes is more complex than previously thought.

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Contributors: OS and GJ had the idea for the study, and GJ was the principal investigator. RTL and PM provided advice in presentation and interpretation of the results. LCS formulated the analysis strategy, carried out all data analyses, and wrote the paper. All authors helped interpret the findings and commented on earlier drafts of the manuscript. All members of the Norwegian Childhood Diabetes Study Group registered newly diagnosed cases of childhood onset type 1 diabetes. LCS and GJ are guarantors.

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Corrections and clarifications

Forest plots: trying to see the wood and the trees
We slipped up with a date in this article by Steff Lewis and Mike Clarke (16 June, pp 1479-80). The date relating to the first use of squares of different sizes to show the positions of the point estimates in forest plots (third paragraph in the "History" section) should be 1988 [not 1998].

Prevention of type 2 diabetes
Although the internet makes it easier to search for articles these days, readers may still have had problems getting hold of references 2 and 3 in this article by K M Venkat Narayan and colleagues (14 July, pp 63-4) as some important details were wrong. The correct volume number for these two references is 344 [not 333], and the correct page numbering for reference 3 is 1390-2 [not 390-2].