Diabetologia (2013) 56:78–81
DOI 10.1007/s00125-012-2731-x

SHORT COMMUNICATION

Fertility in people with childhood-onset type 1 diabetes

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Received: 30 April 2012 / Accepted: 29 August 2012 / Published online: 27 September 2012

Abstract
Aims/hypothesis To assess the number of live births in a population-based, retrospective cohort of women and men with childhood-onset type 1 diabetes, and matched controls.
Methods The reproductive histories of people in a Finnish cohort of 2,307 women and 2,819 men with type 1 diabetes and two matched controls (for each case) were obtained from National Population Register data. All persons with diabetes were diagnosed with the disease in 1965–1979 at the age of 17 or under. A proportional hazards model was used to model the association between the rate of live births as a function of the age of an individual and the observed covariates (sex and age at onset of diabetes).
Results Both women and men with diabetes had a smaller number of live births than the controls; the HR of having a first child for diabetic women compared with controls was 0.66 (95% CI 0.62, 0.71) and for men was 0.77 (95% CI 0.72, 0.83). In women, a birth cohort effect was detected; in more recent birth cohorts, the difference between diabetic women and controls as regards having children was significantly smaller than in earlier cohorts. Later age at onset of diabetes was associated with a higher rate of having a first child among men ($p=0.04$) and having a second live birth among women ($p=0.002$).
Conclusions/interpretation Type 1 diabetes affects the number of live births in both women and men. The age at onset of diabetes is associated with the pattern of reproduction in both diabetic women and men.

Keywords Cohort studies · Diabetes mellitus, type 1 · Erectile dysfunction · Family characteristics · Fertility · Men · Women

Abbreviation
DERI Diabetes Epidemiology Research International

Introduction

Only about 30 years ago, women with type 1 diabetes were often advised not to have any children if they had had the disease for more than 20 years [1]. Very few studies exist on fertility and family size (the number of live births) in people with childhood-onset diabetes. Here, we use the word 'fertility' in its demographic meaning, as the observed number of offspring, not referring to the biological ability to reproduce (which can be called fecundity). The results of previous studies indicate that the fertility of women with type 1 diabetes is lower than that of non-diabetic women [2]. One

Electronic supplementary material The online version of this article (doi:10.1007/s00125-012-2731-x) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

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large study reported that the fertility of diabetic women has increased over time and that this increase was correlated to a drop in diabetic complications [3]. The few and small existing studies on the number of children of diabetic men suggest that there is no difference compared with other men [4, 5].

Our aim was to assess the number of live births of Finnish women and men with childhood-onset diabetes, compare these with those in age- and sex-matched non-diabetic control persons, and assess time trends and birth cohort effects in relation to number of live births.

Methods

A nationwide population-based cohort of childhood-onset type 1 diabetic Finns was initially identified for a study of mortality—the Diabetes Epidemiology Research International (DERI) mortality study [6]. The patients in the DERI study (cases) were diagnosed with type 1 diabetes at 17 years of age or less in 1965–1979 and placed on insulin at diagnosis. In the nationwide registry, 5,166 cases were identified.

We used information from the Population Register Centre and the Death Register of Statistics Finland. The study was approved by the Ethics Committee of the National Institute for Health and Welfare. From the National Population Register, two control people for each diabetic person in the cohort were identified and matched for birth year, geographical birth region and sex. Controls who had either been discharged from hospital with a diagnosis of diabetes mellitus or who had offspring by a partner with diabetes were excluded from our control group. All cases and controls with Down's syndrome were also excluded, as were people who died before the age of 14 years. After all exclusions the data contained information on 2,307 female cases, 4,530 female controls, 2,819 male cases and 5,509 male controls. The offspring were identified through the National Population Register by computer linkage using the unique health insurance number that is assigned to all residents of Finland. Both diabetic women and men and all control persons were followed for having offspring from the age of 14 years, because reproduction was considered highly unlikely before that age. Women were censored at the age of 50 years, death or the end of follow-up (31 December 2007), whichever occurred first. Men were censored at death or the end of follow-up, whichever occurred first. The event of interest was considered to be the live birth of a child. The statistical methods are described in detail in the electronic supplementary material (ESM) text.

Results

The estimated fertility of female cases (average number of children) was 1.10 (95% CI 1.03, 1.15) and that of female controls was 1.83 (95% CI 1.77, 1.87); the estimated difference in fertility between cases and controls was −0.73 (95% CI −0.82, −0.67). The fertility of male cases was 1.21 (95% CI 1.19, 1.24) and that of male controls was 1.57 (95% CI 1.51, 1.61); the estimated difference in fertility between cases and controls was −0.37 (95% CI −0.46, −0.32). The attained family size in diabetic cases was significantly smaller than that in controls (Fig. 1); Pearson's χ^2 test comparing attained family sizes in diabetic and control women: $\chi^2=497.7$, $df=4$, $p<2.2\times10^{-16}$ and Pearson's χ^2 test comparing attained family sizes in diabetic and control men: $\chi^2=157.4$, $df=4$, $p<2.2\times10^{-16}$.

The HRs of having children (first, second, third and fourth child), comparing cases with controls, are shown in Tables 1 and 2. The persons with diabetes were less likely to have a first child than the controls, regardless of sex: HR for women 0.66 (95% CI 0.62, 0.71; $p<0.001$); HR for men 0.77 (95% CI 0.72, 0.83; $p<0.001$). The most prominent difference between the sexes was seen as regards the second child; men with diabetes did not differ from men in the control group when looking at the HR of having a second child.

We detected heterogeneity among women in the HRs of having a first child between birth cohorts (1947–1955, 1956–1960, 1961–1964, 1965–1969 and 1970–1978): the more recent the birth cohort, the smaller the difference between diabetic women and controls (homogeneity test of HRs; $p=0.04$).

Age at onset of diabetes mellitus We divided the cases into four groups according to age at onset of diabetes. For this part of the study, we chose only the birth years 1957–1965 (comprising 50.0% of all subjects with diabetes). In men, the rates of having a first child increased with later onset of type 1 diabetes (p for trend test of HRs=0.04). In diabetic

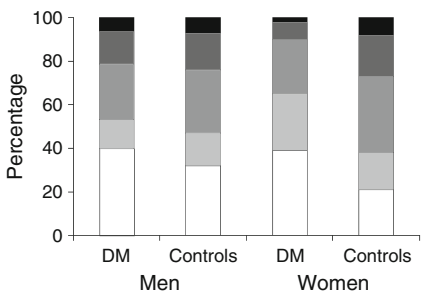

Fig. 1 Attained family sizes in diabetic persons (DM) and controls, separately for men and women. White shading, no children; light grey, one child; mid-grey, two children; dark grey, three children; black shading, four or more children. The y-axis shows the percentage of individuals within each group attaining the number of children indicated by shading. For both men and women, $p<2.2\times10^{-16}$ for DM vs controls

Table 1 Descriptive statistics of female cases and controls; rates of having first, second, third and fourth child (95% CI) plus HRs (95% CI)

Live birth	Births of live children/1,000 person-years among female cases	Subjects with children/total no. of subjects; female cases	Births of live children/1,000 person-years among female controls	Subjects with children/total no. of subjects; female controls	HR for women (HR_w)[a]	*p* values[b]
First child	33 (31, 35)	1,407/2,307	50 (48, 52)	3,567/4,530	0.66 (0.62, 0.71)	2×10^{-16}
Second child	63 (59, 67)	817/1,407	133 (128, 137)	2,816/3,567	0.59 (0.52, 0.68)	1×10^{-14}
Third child	25 (22, 28)	237/817	45 (42, 47)	1,243/2,816	0.75 (0.59, 0.94)	0.02
Fourth+ child	24 (18, 32)	53/237	31 (28, 35)	380/1,243	0.52 (0.25, 1.11)	0.09

[a] *p* value for Wald test for equality of HRs between women and men: first child 0.002, second child 2×10^{-7}, third child 0.71, fourth+ child 0.22

[b] *p* value for Wald test from Cox model stratified by pairs

women, age at onset was not associated with the rates of having a first child, but the rates of having a second child increased with later age at onset (*p* for trend test of HRs= 0.002) (ESM Table 1).

Discussion

The attained number of live births was significantly reduced in men and women with diabetes compared with non-diabetic individuals. The difference in fertility between diabetic individuals and controls was greater among women than among men. The difference in fertility between sexes was statistically significant for the first child, with the level of significance being greater for having a second child. In fact, men with diabetes did not differ from men in the control group when looking at the HR of having a second child. Women with diabetes remained different from the female controls in all categories, except in the category with four or more children.

The difference in number of children between diabetic and non-diabetic women was significantly smaller in more recent birth cohorts. Such a cohort effect was not seen among men. A similar 'normalisation trend' in the fertility of diabetic women was also seen previously in a large Swedish study [3].

This is to our knowledge the first study concerning fertility of both women and men with childhood-onset type 1 diabetes in a large, population-based cohort. Comparison with controls matched for birth year and birth region allowed the differences between diabetic and non-diabetic men and women to be observed. Finland has the highest national incidence of type 1 diabetes in the world [7]. All these factors make this study unique and powerful.

There are potential biological reasons why the ability to reproduce might be reduced in persons with childhood-onset diabetes. According to the results of earlier studies, menstrual problems (e.g. irregularity, long cycles) are more common among diabetic women than in the general population [8]. In men with type 1 diabetes, the prevalence of erectile dysfunction is more common than among non-diabetic men, prevalence increasing with longer disease duration [9]. There are studies indicating impaired semen quality and an increased prevalence of retrograde ejaculation in diabetic men [10].

In our study, the rate of having children was statistically significantly smaller among those men who had been diagnosed with diabetes at an earlier age—which also means a longer duration of the disease. The significance of this difference in fertility according to age at diagnosis of diabetes is diminished by the fact that a younger age at onset in our study design also means a younger age at the end of

Table 2 Descriptive statistics of male cases and controls; rates of having first, second, third and fourth child (95% CI) plus HRs (95% CI)

Live birth	Births of live children/1,000 person-years among male cases	Subjects with children/total number of subjects; male cases	Births of live children/1,000 person-years among male controls	Subjects with children/total number of subjects; male controls	HR for men (HR_m)[a]	*p* values[b]
First child	27 (26, 29)	1,561/2,819	36 (35, 37)	3,769/5,509	0.77 (0.72, 0.83)	2×10^{-13}
Second child	122 (115, 129)	1,132/1,561	135 (130, 140)	2,919/3,769	0.99 (0.86, 1.13)	0.84
Third child	40 (36, 44)	453/1,132	46 (44, 49)	1,295/2,919	0.79 (0.65, 0.95)	0.01
Fourth+ child	32 (27, 38)	136/453	30 (27, 33)	368/1,295	0.94 (0.54, 1.63)	0.82

[a] *p* value for Wald test for equality of HRs between women and men: first child 0.002, second child 2×10^{-7}, third child 0.71, fourth+ child 0.22

[b] *p* value for Wald test from Cox model stratified by pairs

follow-up. This means that some of the study persons, especially the men, had probably not yet had all the children that they intended to. In order to avoid ascertainment bias in estimated HRs, we restricted the study population in this part of the analyses to the birth years 1957–1965 to simultaneously maintain coverage of all ages at onset and maximise average follow-up (to the age of 43–51 years).

The proportion of diabetic men and women who have chosen to remain childless or to have fewer children than desired, specifically because of their diabetes, is unknown. In a Danish study [2] many women with diabetes reported voluntary infertility, but the proportion did not differ significantly from that in the control group. The smaller number of offspring among diabetic women and men in our study might not be due to reduced fecundity.

The possible influence of fear of passing on diabetes to one's children or fear of worsening of diabetic complications by having children is an under-investigated area of interest and calls for other types of studies than register studies. The lower fertility among diabetic men and women can also be influenced by the attitudes of diabetic persons or their treating doctors about the risks of diabetic pregnancies. This is supported by the fact that the difference in fertility between diabetic women and controls is significantly smaller in later birth cohorts—type 1 diabetes per se is no longer regarded as an obstacle to pregnancy.

Acknowledgements The authors thank A. Reunanen (retired from the Institute for Health and Welfare, Helsinki, Finland) for valuable comments on the manuscript and PhD N. Bolton (self-employed) for language revision.

Funding This research was supported by the Wilhelm and Else Stockmann Foundation.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement LS wrote, reviewed and edited the manuscript and participated in the analysis and interpretation of data. JP analysed the data and participated in writing and editing the manuscript. LH was involved in initiating the study, collected data and critically reviewed the manuscript. RK participated in interpreting data, contributed to discussion and reviewed and edited the manuscript. JT initiated the study, was responsible for the conception and design of the study, acquisition and interpretation of data and edited the manuscript. All authors approved the version to be published.

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