Diabetologia (2014) 57:2501–2504
DOI 10.1007/s00125-014-3376-8

SHORT COMMUNICATION

Fertility is reduced in women and in men with type 1 diabetes: results from the Type 1 Diabetes Genetics Consortium (T1DGC)

Julia C. Wiebe · Angelo Santana · Nathan Medina-Rodríguez · Marta Hernández · Javier Nóvoa · Dídac Mauricio · Ana M. Wägner · on behalf of the T1DGC

Received: 23 May 2014 / Accepted: 21 August 2014 / Published online: 14 September 2014

Abstract
Aims/hypothesis A recent Finnish study described reduced fertility in patients with childhood-onset type 1 diabetes. The Type 1 Diabetes Genetics Consortium (T1DGC) is an international programme studying the genetics and pathogenesis of type 1 diabetes that includes families with the disease. Our aim was to assess fertility, defined as number of offspring, in the affected and unaffected siblings included in the T1DGC.
Methods Clinical information from participants aged ≥18 years at the time of examination was included in the present analysis. The number of offspring of affected and unaffected siblings was compared (in families including both) and the influence of birth year, disease duration and age of onset was assessed, the last in affected siblings only, using Poisson regression models.
Results A total of 3010 affected and 801 unaffected adult siblings that belonged to 1761 families were assessed. The mean number of offspring was higher in the unaffected than in the affected individuals, and the difference between the two groups was more pronounced in women than men. Poisson regression analysis showed that both sex and birth cohort significantly affected the differences between groups. In the affected siblings, adult onset (≥18 years), female sex and older birth cohort were associated with higher fertility.
Conclusions/interpretation Patients with type 1 diabetes have fewer children than their unaffected siblings. This effect is more evident in women and in older birth cohorts. Onset of type 1 diabetes as an adult rather than a child is associated with a higher number of offspring, even after accounting for birth cohort and disease duration.

Electronic supplementary material The online version of this article (doi:10.1007/s00125-014-3376-8) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

J. C. Wiebe · J. Nóvoa · A. M. Wägner (✉)
Department of Endocrinology, Complejo Hospitalario Universitario Insular Materno-Infantil, Av Marítima del sur, s/n., 35016 Las Palmas de Gran Canaria, Spain
e-mail: ana.wagner@ulpgc.es

J. C. Wiebe · J. Nóvoa · A. M. Wägner
Instituto de Investigaciones Biomédicas y Sanitarias, ULPGC, Las Palmas de Gran Canaria, Spain

A. Santana (✉) · N. Medina-Rodríguez
Department of Mathematics, Universidad de Las Palmas de Gran Canaria, Edificio de Informática y Matemáticas, Campus Universitario de Tafira, 35017 Las Palmas de Gran Canaria, Spain
e-mail: angelo@dma.ulpgc.es

N. Medina-Rodríguez
IUMA–Information and Communication Systems, ULPGC, Las Palmas de Gran Canaria, Spain

M. Hernández
Department of Endocrinology, Hospital Universitari Arnau de Vilanova, Lleida, Spain

M. Hernández
Institut de Recerca Biomedica de Lleida, Universitat de Lleida, Lleida, Spain

D. Mauricio
Department of Endocrinology, University Hospital Germans Trias i Pujol, Badalona, Spain

D. Mauricio
Health Sciences Research Institute Germans Trias i Pujol, Badalona, Spain

Keywords Fertility · Offspring · Parity · Type 1 diabetes

Abbreviation
T1DGC Type 1 Diabetes Genetics Consortium

Introduction

Type 1 diabetes may negatively affect obstetric and perinatal outcomes. Fertility, defined as number of offspring, is reduced in women with type 1 diabetes [1]. Indeed, although both fertility and the risk of congenital malformations have improved in women with type 1 diabetes in the past few decades [1], pregnancy outcome is still worse than that in healthy women, as is physical and psychological well-being [2]. On the other hand, data about fertility in men with type 1 diabetes are scarce. One recent Finnish population-based study showed a reduced number of offspring both in women and in men with the disease [3].

The Type 1 Diabetes Genetics Consortium (T1DGC) is an international programme that aims to study the genetics and pathogenesis of type 1 diabetes [4, 5]. With thousands of families with at least two affected siblings included from all over the world, this collection represents an extraordinary resource. We aimed to identify differences in the number of offspring of affected and unaffected siblings and to assess the factors that influence fertility.

Methods

Clinical information was obtained by questionnaire at each of the participating centres, whose Ethics Committees had previously approved the study. Only individuals aged ≥18 years at the time of examination were included in the present analysis. To avoid possible effects derived from ethnic differences, white individuals were analysed separately, since they represented 96.4% of the participants. The T1DGC database (2009) contained a total of 3010 affected and 801 unaffected adult siblings, from 1761 white families. Mean age (±SD) was 31.6±11.3 years and 50.3% were women. Analyses were also performed including all ethnicities (1880 families, 3953 participants). Inclusion criteria have been described previously [4, 5].

To compare the number of offspring of affected and unaffected siblings, we restricted our analysis to the 584 families containing both. We randomly selected only one affected and one unaffected sibling from each family, thus reducing potential bias owing to uncontrolled differences in family size, origin and environmental factors. Electronic supplementary material (ESM) Table 1 shows the main features of the affected and unaffected siblings. Comparisons were made using X^2 and Wilcoxon tests. A Poisson regression model was used to analyse the data, in which the response variable was the logarithm of the mean number of offspring, assuming multiplicative effects between the outcome (mean number of offspring) and the explanatory variables (covariates). Disease status (affected or unaffected), sex and birth cohort, as well as the interaction between them, were considered as covariates in the model. Goodness of fit was assessed by the X^2 test (a non-significant result reflects a good fit). An important assumption of this model is that the mean and variance of the data are similar. Overdispersion (variance > mean) was assessed by Dean's test [6].

To assess the influence of time of onset of diabetes on fertility, we analysed the affected siblings ≥18 years at the time of examination who had known time of onset and number of children. We compared affected individuals with adult- and childhood-onset type 1 diabetes (diagnosis at ≥18 and ≤17 years, respectively). To avoid bias due to family structure, this analysis was conducted in two ways. In the first analysis, only one affected sibling was randomly selected per family (1686 unrelated individuals; 684 with adult onset and 1002 with childhood onset). In the second analysis, only families with at least one sibling in each onset category were considered; in these families, one affected sibling with adult onset and one with childhood onset were randomly selected. A Poisson regression model was used to analyse the findings, in which time of onset, birth cohort and sex were considered as covariates. Statistical analyses were performed with the statistical computing environment R v3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Number of offspring of affected vs unaffected siblings ESM Table 2 shows the distribution of the number of offspring according to the sex and diabetes status of the siblings. Overall, women had more children than men, mainly due to a higher proportion of childless men. The mean number of offspring was higher in the unaffected than in the affected siblings, and the difference by diabetes status was greater in women than in men (Fig. 1, ESM Table 2). The fitted model showed a significant effect ($p<0.001$) of all the covariates and of the interactions of disease status with birth cohort ($p<0.012$) and sex ($p=0.0066$). The χ^2 test (p value 0.95) showed a good fit of the data, and Dean's test (p value 0.58) revealed no overdispersion. ESM Table 3 shows the ratio of the number of children of affected siblings vs unaffected siblings, according to sex and birth cohort. It remained below one after adjusting for birth cohort (0.8 [95% CI 0.7, 0.9]), and was lower in women (0.72 [95% CI 0.6, 0.85]) than in men (0.91 [95% CI 0.64, 0.98]). The extent of the difference between the ratios (expressed as ratio of ratios women/men)

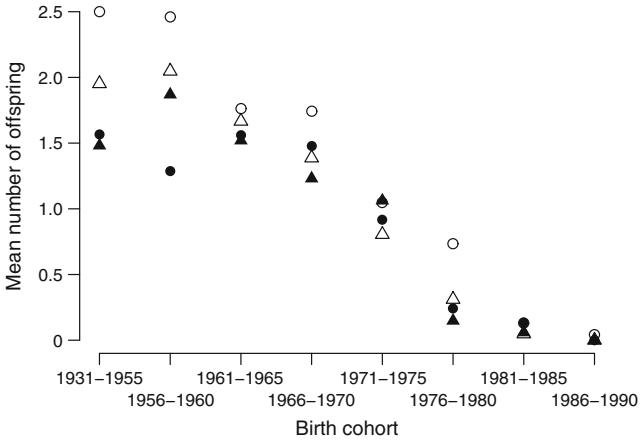

Fig. 1 Mean number of offspring vs birth cohort, sex and type 1 diabetes status. Black symbols, affected individuals; white symbols, unaffected individuals; circles, women; triangles, men

was also significant: 0.79 (95% CI 0.64, 0.98; p=0.033). Overall, similar results were seen when all families (1880, all ethnicities) were included (data not shown).

Effect of age of onset To assess the effect of age of onset of type 1 diabetes on number of offspring, only affected siblings were included, classified by childhood onset or adult onset. The features of these siblings are summarised in ESM Table 4 and the findings are shown in Fig. 2. The Poisson regression model showed a good fit (p=0.999) and lack of overdispersion (p=0.7268). Birth cohort and time of onset had a significant effect on the number of offspring (p<0.001) and there was significant interaction between them (p<0.001), the effect of time of onset decreasing in more recent birth cohorts. There was a significant effect of sex, which also interacted with birth cohort (p=0.011). When included in the model, duration of the disease (at the time of examination) showed no effect (p=0.8838). The adjusted model showed that participants with childhood-onset type 1 diabetes had significantly fewer children than those with adult onset for the cohort born between 1931 and 1955 (Fig. 1, ESM Tables 5–7). When only the 426 families with one sibling with adult onset and another sibling with childhood onset were considered, a significant effect of birth cohort and time of onset was again observed (p<0.001), but no interaction between these variables (p=0.5442) or sex differences (p=0.3866) were found (ESM Fig. 1, ESM Tables 6 and 7).

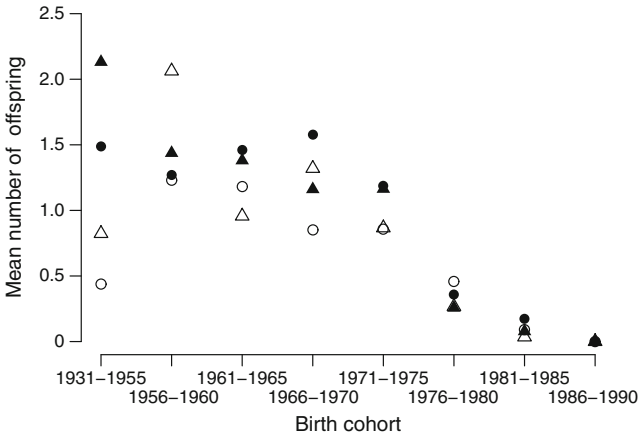

Fig. 2 Mean number of offspring vs birth cohort, sex and time of onset of type 1 diabetes. Black symbols, adult onset; white symbols, childhood onset; circles, women; triangles, men

Discussion

Our data show that type 1 diabetes significantly affects fertility. Women and men with type 1 diabetes had significantly fewer offspring than their unaffected siblings. This reduction was significant for some birth cohorts, but not all, and tended to be more pronounced in women. Given that we selected families with both affected and unaffected siblings, we can reasonably argue that both groups were exposed to similar environmental factors, including socioeconomic status. Therefore, we may assume that differences in the number of offspring were primarily due to the presence of type 1 diabetes.

To the best of our knowledge, this is the first international study to assess the number of offspring in both women and men with type 1 diabetes that has included both childhood and adult onset of the disease. Our results confirm those of previous German, Swedish and Finnish studies [1, 3, 7]. A German study in patients with type 1 diabetes (age of onset 23± 15 years) also described a reduced fertility rate in women (0.88) and an even lower rate in men (0.65), compared with a rate of 1.36 in the background female population. More male than female patients were childless at the age of 41–45 years, but there was no available information about childlessness in the male background population [7]. Similarly, reduced fertility was observed in a population-based Swedish study that included women with childhood onset of type 1 diabetes [1] and in a recent Finnish study that included both women and men [3]. In the Finnish study, in agreement with our findings, the reduction in fertility with type 1 diabetes was larger in women than in men. Furthermore, an influence of birth cohort on fertility was also found in the Finnish and Swedish studies, showing a 'normalisation trend' in later birth cohorts [1, 3]. Indeed, the Swedish study concludes that it appears that normalisation in fertility has occurred among women with uncomplicated type 1 diabetes and an onset in the past 20 years [1]. Our results do not refute these findings.

In affected participants, we observed that fertility was significantly lower in those with childhood onset of type 1 diabetes (Fig. 2), whereas duration of the disease at examination did not itself have an effect. This might be due to the fact that birth cohort was included in the model and, therefore,

duration of the disease was somewhat already accounted for. Furthermore, we cannot rule out an effect of participants developing type 1 diabetes after having a child, because date of birth of the offspring was not available.

Since no further information is available on voluntary or involuntary childlessness, complications or glycaemic control, we can only speculate on the reasons for the differences in fertility. Biological reasons, such as menstrual irregularities and erectile dysfunction, could be part of the explanation. Furthermore, women with diabetes may be discouraged by pregnancy risks and intensive, time-consuming follow-up. However, regardless of the causes, the difference in fertility between patients with type 1 diabetes and the non-diabetic population seems to be diminishing over time.

In conclusion, individuals with type 1 diabetes have fewer children than their unaffected siblings and this effect is more pronounced in women and in older birth cohorts. In patients with type 1 diabetes, later age of onset of diabetes is associated with a higher number of offspring.

Funding This research uses resources provided by the T1DGC, a collaborative clinical study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Allergy and Infectious Diseases, National Human Genome Research Institute, National Institute of Child Health and Human Development, and Juvenile Diabetes Research Foundation International (JDRF) and supported by U01 DK062418. The authors are being or have been supported during the performance of the study by the European Foundation for the Study of Diabetes (EFSD; Albert Renold Travel Grant 2013 [NMR] and EFSD/Novo Nordisk/JDRF 2008 Programme for Type 1 Diabetes [JCW, JN and AMW]) and Instituto de Salud Carlos III (PI08/1113, PI11/02441, PI10/02310 and PI06/1104 [JCW, JN, DM, MH and AMW]).

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

Contribution statement JCW made substantial contributions to the conception and design of the study and wrote and edited the manuscript. AS analysed and interpreted the data and wrote the manuscript. NMR analysed the data and revised the manuscript. JN, MH and DM collected data and critically reviewed the manuscript. AMW participated in the design of the study, data collection and interpretation and wrote the manuscript. All authors reviewed and accepted the final version of the manuscript. AMW and AS are guarantors of this work.

References

1. Jonasson JM, Brismar K, Sparén P et al (2007) Fertility in women with type 1 diabetes: a population-based cohort study in Sweden. Diabetes Care 30:2271–2276
2. Dalfrà MG, Nicolucci A, Bisson T, Bonsembiante B, Lapolla A (2012) Quality of life in pregnancy and post-partum: a study in diabetic patients. Qual Life Res 21:291–298
3. Sjöberg L, Pitkäniemi J, Haapala L, Kaaja R, Tuomilehto J (2013) Fertility in people with childhood-onset type 1 diabetes. Diabetologia 56:78–81
4. Rich SS, Concannon P, Erlich H et al (2006) The type 1 diabetes genetics consortium. Ann N Y Acad Sci 1079:1–8
5. Wägner AM, Mauricio D, Argente J et al (2005) Red Europea de Genética de la Diabetes Tipo 1. Endocrinol Nutr 52:177–183, article in Spanish
6. Dean CB (1992) Testing for overdispersion in Poisson and binomial regression models. J Am Stat Assoc 87:451–457
7. Holstein A, Patzer O, Tiemann T, Vortherms J, Kovacs P (2012) Number and sex ratio of children and impact of parental diabetes in individuals with type 1 diabetes. Diabet Med 29:1268–1271