Age at menopause in women with type 1 diabetes mellitus: the OVADIA study

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STUDY QUESTION: Is type 1 diabetes a determinant of advanced ovarian ageing, resulting in an early age at natural menopause?

SUMMARY ANSWER: No clear evidence was provided that type 1 diabetes is a determinant of accelerated ovarian ageing resulting in an early menopause.

WHAT IS KNOWN ALREADY: The association between type 1 diabetes and early menopause has been examined previously with inconsistent results.

STUDY DESIGN, SIZE, DURATION: A cross-sectional study was performed in 140 post-menopausal women with, and 5426 post-menopausal women without, diabetes.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Both women with and without diabetes had experienced natural menopause. Study participants filled out a standardized questionnaire including report of their age at last menstrual period. Differences in menopausal age were analysed using linear regression analyses, with adjustment for possible confounders.

MAIN RESULTS AND THE ROLE OF CHANCE: Mean age at natural menopause was 49.8 ± 4.7 years in women with type 1 diabetes and 49.8 ± 4.1 in women without diabetes. Linear regression analyses showed that type 1 diabetes was not associated with an earlier menopause compared with the reference group without diabetes, after adjustment for age, smoking history and parity (difference in age at menopause between women with type 1 diabetes and reference group 0.34 years, 95% confidence interval −0.34, 1.01).

LIMITATIONS, REASON FOR CAUTION: Age at menopause was self-reported and assessed retrospectively. We had no information regarding microvascular complications therefore a possible association between vascular health and menopausal age could not be investigated.

WIDER IMPLICATIONS OF THE FINDINGS: It has been hypothesized that the possible mechanism behind an accelerated ovarian ageing process in type 1 diabetes is prolonged poor glycaemic control and subsequent effects on vascular health. The improved glycaemic control during the last decades may have prevented vascular damage from occurring to an extent that would affect organ function. Nevertheless, the present findings are reassuring for reproductive health prospects in women with type 1 diabetes.

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Key words: type 1 diabetes / age at menopause / ovarian ageing / natural menopause / vascular health

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Introduction

Menopause is defined as the permanent cessation of menstrual cyclicity resulting from follicle pool depletion in the ovaries. This clinical diagnosis is made after 12 consecutive months of amenorrhea and occurs at a mean age of 51 years, although age at menopause varies widely between 40 and 60 years (Lambalk et al., 2009).

Timing of menopause has substantial implications for women’s health and fertility. Early menopause has been associated, among others, with a moderately increased risk of cardiovascular disease (van der Schouw et al., 1996; Jacobsen et al., 1997; Ossewaarde et al., 2005; Atsma et al., 2006; Lisabeth et al., 2009) and type 2 diabetes (Brand et al., 2013). However, the prevailing theory that estrogen depletion causes this advanced vascular ageing has been challenged based on observations that estrogen replacement therapy does not prevent and possibly even enhances the development of cardiovascular disease in postmenopausal women (Rossouw et al., 2002). These findings have led to the reverse hypothesis that it is not the lack of estrogen that causes cardiovascular damage, but that vascular compromise itself is a driving factor in the pathogenesis of ovarian ageing (Kok et al., 2006).

Women with type 1 diabetes are at risk of premature morbidity and mortality from cardiovascular disease (Nathan, 1993; Nishimura et al., 2001; Klein et al., 2004; Schnell et al., 2013). We therefore hypothesized that premature vascular ageing due to type 1 diabetes precedes ovarian ageing, resulting in an early menopause. One study suggested that women with type 1 diabetes are at risk to experience early depletion of the ovarian follicle pool, resulting in menopause at a younger age compared with women without diabetes (Dorman et al., 2001), although this observation was not supported by later reports (Sjöberg et al., 2011; Kim et al., 2014).

Women with type 1 diabetes are reported to have a delayed age at menarche (Rohrer et al., 2007) and are at higher risk for menstrual irregularities (Codner et al., 2006; Snell-Bergeon et al., 2008) compared with women without diabetes of similar age. Combined with an earlier age at menopause, these women may be subjected to a 6-year reduction in reproductive years (Dorman et al., 2001).

As all previous studies have important methodological shortcomings, it is urgently needed to confirm a possible early decay in ovarian reserve in women with type 1 diabetes.

In the present study we aimed to confirm the earlier reported difference in age at natural menopause in women with type 1 diabetes compared with women without diabetes.

Materials and Methods

Study design

A cross-sectional study was performed in 140 women with type 1 diabetes included in the OVarian Ageing in type 1 DIAbetes mellitus (OVADIA) study. The Prospect-Epic cohort of Dutch women was used as reference population of women without diabetes. This study has been registered at http://www.clinicaltrials.gov under NCT01665716.

Study population

Patients with type 1 diabetes were recruited from the department of Internal Medicine of several Dutch hospitals around the country. Invitation letters were sent until 140 women with type 1 diabetes agreed to participate. Also, patients were recruited through the Dutch Diabetes Society (Advertisements in newsletter and on website). Caucasian women at least 51 years old with type 1 diabetes who had experienced a natural menopause were considered eligible for the study. Exclusion criteria were an induced menopause, i.e. hysterectomy, ovarian surgery, chemo- or pelvic radiation therapy, endometrial ablation or perimenopausal use of hormones. A total of 590 potentially eligible women were identified. These women were sent a letter of invitation explaining the nature of the study. In total, 323 women (55%) responded of whom 80% was willing to consider participation. After sending these women the detailed study information, they were screened for in- and exclusion criteria by telephone. Overall, 45% did not fulfill the inclusion criteria, i.e. 16% had an induced menopause, 19% had an unknown menopausal status due to perimenopausal exogenous hormone use or could not recall age at menopause and 10% had not yet experienced the full 12 consecutive months of amenorrhea. As depicted in Fig. 1, this resulted in 140 women who were sent the study questionnaire and consent forms.

Type 1 diabetes was defined according to the clinical criteria applied at that time.

The study was carried out in accordance with the Declaration of Helsinki and approval was obtained from the Institutional Review Board of the University Medical Center Utrecht (UMCU) and all participants provided written informed consent prior to inclusion.

As a reference group of women without diabetes, the Prospect-Epic cohort was used. The design and rationale of this study has been described previously (Boker et al., 2001).

In brief, the cohort comprises 17357 Caucasian women living in the Netherlands, aged 49–70 years. Women were invited to participate in the study through the national breast cancer screening between 1993 and 1997. At enrolment, all participants underwent a physical examination and filled out detailed questionnaires about dietary, reproductive and medical history. To ensure comparability with the diabetes group, for the current study we selected women of at least 51 years of age who had experienced natural menopause. Excluded were 67% of the women who were premenopausal (n = 3497), had a surgical menopause (n = 4449), used hormones during the menopausal transition (n = 2161), with an unknown menopausal status or age (n = 1194), with diabetes mellitus (n = 343) or who were younger than 51 years at inclusion (n = 287), resulting in a total of 5426 women available for analysis.

Study parameters

Data on health issues, such as medication use and smoking history, and reproductive history were collected by a questionnaire. Women were asked about their age at menarche and subsequent menstrual cycle pattern, i.e. the time it took until the menstrual cycle became regular. Furthermore they reported the number of live born children, use of hormonal contraceptives and age at last menstrual period.

The primary outcome measure was age at natural menopause, defined according to the World Health Organization as amenorrhea for at least 12 consecutive months without other obvious reasons.

Statistical analysis

Descriptive parameters and population characteristics were reported for women with and without diabetes as mean ± SD and categorical data were expressed as percentages.

The distribution of age at menopause was depicted graphically in a boxplot for both women with and without diabetes. Linear regression analyses were used to compare mean age at menopause, with 95% confidence intervals (CI) between women with and without diabetes. Adjustments were made for age at questionnaire, smoking history (ever/never smoking) and nulliparity. To correctly model a possibly non-linear relationship between
age at questionnaire and age at menopause, a restricted cubic spline with three knots was used.

In addition, a sensitivity analysis was performed restricted to women with diabetes diagnosed before age 35 years ($n = 96$) to ensure sufficient duration of disease. The second sensitivity analysis was restricted to women who developed a normal regular menstrual cycle within 5 years after menarche ($n = 109$ with diabetes and $n = 4469$ without diabetes), in order to exclude women with possible polycystic ovary syndrome (PCOS) (Treloar et al., 1967) who are suggested to reach menopause at a later age than women with regular menstrual cycles (Piltonen et al., 2005).

A difference in menopausal age of 1 year ($SD = 4.1$ years) between women with and without type 1 diabetes was considered a relevant finding. To ensure the statistical significance of such a difference with a reference group of 5800 women, a total of 137 women with type 1 diabetes was needed, using an $\alpha = 0.05$ and $\beta = 0.80$.

Data were analysed using SPSS for Windows, version 20.0 (SPSS, Inc., Chicago, IL, USA) and R version 2.10.0 (http://www.r-project.org).

**Results**

Population characteristics of the women with and without diabetes are presented in Table I. Both groups were comparable in terms of age at questionnaire (59.9 years versus 60.0 years). In addition, parity and smoking behaviour were comparable across both groups. The median age [Interquartile Range] at diagnosis of diabetes was 28.0 [22.5] years.

**Age at menopause**

Mean age at natural menopause was 49.8 ± 4.7 years in women with type 1 diabetes and 49.8 ± 4.1 in women without diabetes, as depicted in Fig. 2. After adjustment for age, smoking history and parity, women with type 1 diabetes had a non-significant 0.34 years (95% CI = −0.34, 1.01) higher age at menopause than women without diabetes (Table II).

Sensitivity analyses excluding all women with diabetes diagnosed after 35 years did not materially change these results (difference in age at menopause 0.42 years 95% CI = −0.39, 1.24). The same was true for the sensitivity analyses excluding those women with a possible PCOS. Women with type 1 diabetes had a non-significant 0.05 years (95% CI = −0.80, 0.71) earlier menopause than women without diabetes, after adjustment for confounders (Supplementary Table SI).

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**Table I** Population characteristics of women with and without type 1 diabetes.

<table>
<thead>
<tr>
<th></th>
<th>With diabetes $n = 140$</th>
<th>Without diabetes $n = 5426$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at questionnaire (years)</td>
<td>59.9 ± 6.9</td>
<td>60.0 ± 5.1</td>
</tr>
<tr>
<td>Age at menarche (years)</td>
<td>13.8 ± 3.6</td>
<td>13.5 ± 1.6</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>25 (18%)</td>
<td>789 (15%)</td>
</tr>
<tr>
<td>Ever smoker, n (%)</td>
<td>85 (61%)</td>
<td>3803 (70%)</td>
</tr>
<tr>
<td>Age at diagnosis of diabetes (years)</td>
<td>28.0 ± 14.2</td>
<td>—</td>
</tr>
</tbody>
</table>

Data are presented in mean ± SD or number (%).
Figure 2  Boxplot distribution of age at natural menopause for women with and without type 1 diabetes. Mean age at natural menopause was 49.8 ± 4.7 years in women with type 1 diabetes and 49.8 ± 4.1 in women without diabetes. Difference in age at menopause in women compared to women without diabetes is −0.02 years, 95% confidence interval (−0.72, 0.67).

Table II  Linear regression analysis comparing age at menopause in women with and without diabetes.

<table>
<thead>
<tr>
<th>Difference in age at menopause (years)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>With diabetes versus without diabetes</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>−0.02</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>0.27</td>
</tr>
<tr>
<td>Adjusted for age and smoking</td>
<td>0.31</td>
</tr>
<tr>
<td>Adjusted for age, smoking and nullparity</td>
<td>0.34</td>
</tr>
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Regression coefficient with 95% confidence interval (CI).

Discussion

The present study does not confirm an earlier observation that women with type 1 diabetes experience menopause earlier than women without diabetes. This implies that the current hypothesis that the process of ovarian ageing is accelerated in women with type 1 diabetes may have to be rejected.

The current study results are in line with a previous study, which also could not detect an early menopause in women with type 1 diabetes (Sjoberg et al., 2011). Sjoberg et al. studied a large population-based cohort of Finnish women with childhood-onset type 1 diabetes who were at least 40 years old when questioned about their age at last menstrual period and reported a median age at menopause of 52.5 years (Sjoberg et al., 2011). Factors associated with an earlier menopause were the presence of end-stage renal disease and proliferative retinopathy. However, median age at menopause in the women with type 1 diabetes was compared with a population estimate, thereby lacking the adjustment for possible confounders in the comparison of menopausal age.

The Diabetes Control and Complication Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study is a multicentre, randomized controlled clinical trial, designed to compare the impact of intensive diabetes treatment on the development and progression of early microvascular complications in type 1 diabetes (Kim et al., 2014). In this study 240 women had reached natural menopause and mean age at menopause did not differ between the intensive treatment and conventional treatment groups. In secondary analyses, glycaemic control and microvascular complications were not related to age at menopause in this study, but an increase in the required insulin dosage decreased risk of natural menopause (hazard ratio 0.91, 95% CI 0.75–0.98).

These results are all in contrast with one previous large cohort study, the Familial Autoimmune and Diabetes (FAD) study, reporting that women with type 1 diabetes had a two times higher risk to experience menopause compared with women without diabetes (Dorman et al., 2001). In this study, adults with type 1 diabetes and controls, both related and unrelated, were included in 1981 to study mortality in type 1 diabetes. During follow-up rounds in 1990 and 1993 data on menstrual cycles and age at menopause were assessed by questionnaires.

Possible explanations for these conflicting results in comparison to our study may lie in the age at which menopause was assessed. In the FAD study, women had an average age of 42 years and therefore only a small proportion had reached menopause (~10%) (Dorman et al., 2001). As a result, the distribution of menopausal age becomes left-skewed as only those who have experienced an early menopause are represented. Moreover, to accelerate the ovarian ageing process, in terms of an earlier age at menopause, prolonged poor glycaemic control and subsequent effects on vascular health have been proposed as the possible mechanism behind the link between ovarian ageing and type 1 diabetes. The improved glycaemic control during the last decades may have prevented vascular damage from occurring to an extent that would affect organ function. Indeed, microvascular complications have been suggested as the cause of the advanced ovarian ageing process in women with type 1 diabetes (Sjoberg et al., 2011). Intensive glycaemic control, which is currently considered standard therapy, reduces both micro- and macrovascular complications in type 1 diabetes (The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group, 2000; Nathan et al., 2005). As a result, an accelerating effect of type 1 diabetes on age at menopause onset may currently be prevented by adequate treatment, and therefore no longer be observed. However, the study of Kim et al. did not find an earlier menopause in women on conventional treatment when compared with intensive treatment (Kim et al., 2014).

On the other hand, women with poor glycaemic control and early vascular compromise and subsequently an early menopause may not have been included in the study population due to early mortality. As sampling started from 51 years onwards, such selection bias may have masked any effect of diabetes on age at menopause. Notably, the relative risk of mortality is evidently higher in women with type 1 diabetes younger than 51 years compared with those without diabetes. The absolute mortality rate, however, remains very low due to tight glucose control (Livingstone et al., 2012). Therefore, although potentially present, the role for such bias may be considered small.
The strength of this study lies in the direct comparison of the group with type 1 diabetes with a population-based reference cohort without diabetes. Both groups consist of only naturally post-menopausal women, which could lead to selection bias due to the exclusion of both women who have not yet reached menopause and women who had a surgical menopause. As the age at assessment of menopausal age is on average 60 years and comparable between the women with and without diabetes, we do not feel this could have led to an underestimation of the menopausal distribution as presented. The lower percentage of surgical menopause in the diabetes group compared with the reference group (15 versus 26%) is likely to reflect recent trends towards a more conservative approach in applying surgery in women with menstrual disturbances.

In addition, other known factors, such as the distribution of parity and smoking, have been controlled for. Notably, these factors may have been subjected to time effects, where parity and smoking prevalence were likely to be higher in the earlier cohort. The net effect on age at menopause however, lower for smokers while higher for parous women, cannot be estimated. Finally, unknown factors that may have influenced menopausal age distribution are not very likely to be present, given the stability of age at menopause over very long time periods. Therefore, overall, we do not feel that a more recently assembled cohort without diabetes would have ensured a more solid comparison of the menopause distribution.

A limitation of the present study is the lack of information with regard to microvascular complications, which would have enabled us to investigate the possible association between vascular health and menopausal age.

Nevertheless, the present findings are reassuring for reproductive health prospects in women with type 1 diabetes. In conclusion, the present study demonstrates that women with type 1 diabetes are not at risk to experience an earlier menopause than normal.

Supplementary data
Supplementary data are available at http://humrep.oxfordjournals.org/.

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Authors’ roles
F.Y. recruited the patients, carried out all necessary data analyses and wrote the manuscript. Y.T.v.d.S., H.W.d.V., M.J.C.E. and F.J.M.B. designed the trial, participated in the interpretation of the data and provided significant revisions. A.F. and W.S. reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interest
F.Y., Y.T.v.d.S., H.W.d.V., A.F., M.J.C.E. and W.S. have nothing to disclose. F.J.M.B. has received fees and grant support from the following companies: Ferring, Gedeon Richter, Merck Serono, Medical Specialties Distributors, and Roche.

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