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ARTICLE

Pregnancy loss is associated with type 2 diabetes: a nationwide case–control study

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Abstract

Aims/hypothesis Type 2 diabetes is killing more people than ever, and early-life predictors remain critical for the development of effective preventive strategies. Pregnancy loss is a common event associated with later atherosclerotic disease and ischaemic heart failure and might constitute a predictor for type 2 diabetes. The objective of this study was to investigate whether pregnancy loss is associated with later development of type 2 diabetes.

Methods Using a Danish nationwide cohort, we identified all women born from 1957 through to 1997 and who had a diagnosis of type 2 diabetes during the period 1977 to 2017. The women were matched 1:10 on year of birth and educational level to women without diabetes in the general Danish population. Conditional logistic regression models provided odds ratios for type 2 diabetes with different numbers of pregnancy losses.

Results We identified 24,774 women with type 2 diabetes and selected 247,740 controls without diabetes. Women who had ever been pregnant (ever-pregnant women) with 1, 2 and ≥ 3 pregnancy losses had ORs of type 2 diabetes of 1.18 (95% CI 1.13, 1.23), 1.38 (95% CI 1.27, 1.49) and 1.71 (95% CI 1.53, 1.92) compared with ever-pregnant women with no pregnancy losses, respectively. Women who never achieved a pregnancy had an OR of type 2 diabetes of 1.56 (95% CI 1.51, 1.61) compared with ever-pregnant women with any number of losses. Similar results were found after adjustment for obesity and gestational diabetes.

Conclusions/interpretation We found a significant and consistent association between pregnancy loss and later type 2 diabetes that increased with increasing number of losses. Thus, pregnancy loss and recurrent pregnancy loss are significant risk factors for later type 2 diabetes. Future studies should explore whether this association is due to common background factors or whether prediabetic metabolic conditions are responsible for this association.

Keywords Miscarriage · Pregnancy loss · Recurrent pregnancy loss · Reproduction · Type 2 diabetes

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Research in context

What is already known about this subject?

- Early-life predictors for type 2 diabetes remain critical for the development of effective preventive strategies
- Previous studies document pregnancy losses as predictors of later atherosclerotic disease and ischaemic heart failure

What is the key question?

- Is pregnancy loss associated with later type 2 diabetes?

What are the new findings?

- Our study found a strong and consistent association between pregnancy loss and type 2 diabetes
- The risk for later type 2 diabetes increased with number of pregnancy losses and the results were robust to adjustment for obesity and gestational diabetes
- The association was strongest in women with a high likelihood of euploid pregnancy losses and a suspected immunological aetiology behind their losses

How might this impact on clinical practice in the foreseeable future?

- A follow-up strategy using HbA_{1c} measurements, similar to that used in women with gestational diabetes, could perhaps prove beneficial to women with ≥3 pregnancy losses

Introduction

The global prevalence of diabetes is 8.5% and 1.6 million deaths per year are estimated to be directly caused by diabetes [1]. Type 2 diabetes represents 90% of all diabetes. Lifestyle modifications and drug interventions have the potential to prevent type 2 diabetes [1], which underlines the importance of predictors. Identified predictors for type 2 diabetes include childhood obesity and gestational diabetes [2, 3]. Predictors for diabetes related to pregnancy are an opportunity for identifying women at an increased risk of developing diabetes and for introducing timely preventive actions.

About one in four wanted pregnancies end in a pregnancy loss [4], corresponding to approximately 1 million losses in the USA every year [5]. A pregnancy loss is defined as the spontaneous demise of a pregnancy prior to 22 weeks of gestation [6]. Approximately 60% of all pregnancy losses are assumed to be due to fetal aneuploidy [7]. For the remaining 40% euploid losses, the causes may be due to fetal chromosomal microdeletions, point mutations, structural abnormalities and/or paternal or maternal factors. With increasing number of pregnancy losses, the frequency of euploid pregnancy losses increases [8] and the chance of subsequent live birth decreases [9]. Recurrent pregnancy loss is most frequently defined as three consecutive losses [10, 11] affecting 1–2% of women trying to conceive. Maternal immunity is documented to be associated with recurrent pregnancy loss [9, 12–22], suggesting that low-grade inflammation is involved in recurrent pregnancy loss.

With increasing maternal age, the proportion of aneuploid losses increases and therefore other factors are assumed to play a role in women with ≥3 consecutive pregnancy losses before age 30. Similarly, second trimester pregnancy losses and stillbirths are rarely due to fetal chromosomal anomalies. Recurrent pregnancy loss is associated with immunological disturbances and certain human HLA class II tissue types are associated with the prognosis [14, 19, 22, 23]. Abnormal maternal immune response against male specific antigens [14, 17, 19], more frequently found after a complicated delivery [21], is a possible pathophysiological pathway for recurrent pregnancy loss.

Previous studies document pregnancy losses as predictors of later atherosclerotic disease and ischaemic heart failure [24–26]. Cardiovascular disease and type 2 diabetes share many risk factors but only few studies have investigated the association between pregnancy loss and type 2 diabetes [27, 28]. A recent prospective study among well-educated women found pregnancy loss to be positively associated with later maternal type 2 diabetes [27]. To our knowledge no previous study has investigated the association between recurrent pregnancy loss and type 2 diabetes.

The aim of this study was to investigate if pregnancy loss is associated with later type 2 diabetes. Additionally, we wanted to explore the risk of type 2 diabetes in predefined subgroups of women with a high risk of euploid pregnancy losses and subgroups likely to have an immunological background for their pregnancy losses.

Research design

To study whether pregnancy loss constitutes an early marker of later diabetes we chose a cohort study design with a nested case–control analysis. This design allows us to identify women with type 2 diabetes (cases) and then look back at their reproductive history (nested case–control study). The cases were matched on educational level and birth year. When matching on birth year we ensured that cases and controls have similar risk time (follow-up).

Methods

Data sources Several comprehensive and validated national registers exist in Denmark. All Danish citizens, at birth or immigration, are provided with a unique and permanent identification number and this number is registered at any contact with the healthcare system. All information regarding hospitalisation, medication, morbidity and mortality is recorded in national databases under the unique personal identification number, permitting cross-referencing of data between registers at an individual level. The Danish Civil Registration System was established in 1968 and contains information about date of birth, sex, vital status, parents and immigration and emigration status, updated daily [29]. All information on the date, cause and type of all hospitalisations and surgical procedures have since 1977 been recorded in The Danish National Health Register. All diagnoses are coded according to the International Classification of Diseases (ICD); ICD-8 from 1977 to 1994 and ICD-10 (http://apps.who.int/classifications/icd10/browse/2016/en) from 1994 onward [30]. The Danish Medical Birth Register was established in 1973 and contains data on all births including information on birthweight, length, gestational age and personal identification number of parents [31]. Maternal pre-pregnancy BMI has been recorded in the birth register since 2004. Since 1995, medicine dispensed from Danish pharmacies has been registered in The Danish National Prescription Register, coded according to the Anatomical Therapeutic Chemical Classification System [32]. Pharmacies are mandated by law to register information about all filled prescriptions and the register is considered complete from 1995 and onward [32].

Study population The nationwide cohort comprised 123,603 women with a type 2 diabetes diagnosis in the period 1977–2017. Women born between 1957 and 1997 constituted the case group. Women born in these years were chosen in order to ensure full registered reproductive history up until the type 2 diabetes diagnosis date (women were a minimum 20 years of age when the registers were established [women born in 1957], and at least 20 years of age when the study ended [women born in 1997]) (electronic supplementary material [ESM] Fig. 1). The definition of type 2 diabetes was based on an extraction algorithm for chronic diseases published by The Danish Health Data Authority [33]. The extraction algorithm for type 2 diabetes used in this study is provided in ESM Table 1. The age at diagnosis of type 2 diabetes was determined as the first hospital contact with a diabetes discharge diagnosis or a first filled prescription of glucose-lowering drugs, whichever came first. For each case, ten female birth year- and education-matched controls without type 2 diabetes were randomly selected from the Danish general population using an exact matching algorithm, where cases could not be used as controls. The index date was the date at which type 2 diabetes was recorded for the first time, and for controls, the index date was the date of diagnosis for their matched case.

Study exposures Number of pregnancy losses constituted the exposure of interest. Study exposures before the index date were recorded for all women by cross-referencing data with the national registers on an individual level. We categorised pregnancy loss as the total number of pregnancy losses before the index date; 0, 1, 2 or ≥3 pregnancy losses. We further divided women with no pregnancy losses into women who had achieved a pregnancy (had a live birth, stillbirth, molar pregnancy, ectopic pregnancy or induced abortion), and women who had never achieved a pregnancy. The study exposures were defined based on the clinical diagnosis codes identified in the Danish National Health Register and birth records in the Danish Medical Birth Register. Stillbirth is defined as fetal death after 22 weeks of gestation. An overview of the included codes is provided in ESM Table 2.

Educational level was extracted from the Danish Register of Education. This register contains information on all completed educational degrees. We recorded educational level as below bachelor degree or bachelor degree or higher.

Predefined subgroups of interest On the basis of a priori knowledge of groups with higher likelihood of euploid losses and, in addition, a higher likelihood of pregnancy losses with a higher risk of an immunological background, we created the following subgroups of interest: (1) ≥3 pregnancy losses before age 30; (2) ≥2 pregnancy losses in the second trimester; (3) ≥1 stillbirth; (4) recurrent pregnancy loss (i.e. ≥3 consecutive pregnancy losses); (5) primary recurrent pregnancy loss (≥3 consecutive pregnancy losses without prior live birth); (6) secondary recurrent pregnancy loss (≥1 live birth followed by 3 consecutive pregnancy losses); (7) ≥1 live birth of a boy followed by recurrent pregnancy loss; (8) ≥1 live birth of a girl followed by recurrent pregnancy loss; and (9) ≥1 complicated delivery (i.e. pre-eclampsia, intrauterine growth restriction, placental abruption or preterm birth) followed by recurrent pregnancy loss.

Statistical analyses Baseline characteristics were compared using the χ^2 test and the Mann–Whitney *U* (Wilcoxon) test. Conditional logistic regression models were used to calculate odds ratios with 95% CI for the binary outcomes pertaining to pregnancy loss. Women with pregnancy losses were compared with ever-pregnant women with no losses. Never-pregnant women were compared with ever-pregnant women with any number of losses. Since obesity could be a potential confounder, we conducted a subgroup analysis on women with information about BMI with adjustment for obesity. Information on BMI was extracted from the Danish Medical Birth Register and obesity was defined as BMI> 30 kg/m^2. If a woman ever had a BMI> 30 kg/m^2 in relation to pregnancy (also after index) she was recorded as obese. Finally, we conducted a subgroup analysis in women who achieved pregnancy where we adjusted for gestational diabetes as this is a known predictor for type 2 diabetes. Information on gestational diabetes was extracted from The Danish National Health Register with the relevant ICD codes (ESM Table 2). *p* values <0.05 were considered statistically significant. Data programming was performed using SAS Version 9.4 (SAS Institute, NC, USA) and Stata Version 15 (StataCorp, College Station, TX, USA, https://www.stata.com) and all analyses were performed using R Version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria, https://www.r-project.org).

Ethics The project was approved by the Danish Data Protection Agency (Journal number 2006-41-6907). Data were made accessible at an encrypted individual level. Register studies in Denmark do not require approval from ethics committees. All data are held by Statistics Denmark, which also has administrative rights of the data.

Results

After excluding women with residence outside Denmark for more than 6 months of fertile age, women who died before age 45, women born before 1957 or after 1997, we included 24,774 women diagnosed with type 2 diabetes (Fig. 1), constituting our case population. Similarly, we identified a control population without type 2 diabetes from the Danish general population using the same exclusion criteria as Fig. 1. After matching, the control population included 247,740 women without type 2 diabetes. Age at index date and educational level were similar in the two groups indicating sufficient matching (Table 1). Significantly more women in the case group had a history of gestational diabetes, family history of diabetes, cardiovascular disease, obesity and hypertension.

Figure 2 shows the frequency of pregnancy loss among ever-pregnant cases and controls. A total of 12,613 (74.5%) of the cases and 145,999 (78.7%) of the controls never experienced a pregnancy loss. Women with 1, 2 and ≥ 3 pregnancy losses constituted 3227 (19.1%), 729 (4.3%) and 358 (2.1%) of the cases and 31,144 (16.8%), 5981 (3.2%) and 2402 (1.3%) of the controls, respectively. Women with 1, 2 and ≥ 3 pregnancy losses had ORs of type 2 diabetes of 1.18 (95% CI 1.13, 1.23), 1.38 (95% CI 1.27, 1.49) and 1.71 (95% CI 1.53, 1.92) compared with ever-pregnant women with no losses, respectively. In the case group, 7847 (31.7%) never achieved a pregnancy compared with 62,214 (25.1%) in the controls. Women who had never achieved a pregnancy had an OR of type 2 diabetes of 1.56 (95% CI 1.51, 1.61) compared with ever-pregnant women with any number of losses.

Subgroup analyses Table 2 shows the analysis in women with information about BMI after adjustment for obesity. The analysis included 3064 cases and 42,276 controls. After adjustment for obesity, women with 1, 2 and ≥ 3 pregnancy losses still had significantly increased ORs for type 2 diabetes of 1.40 (95% CI 1.25, 1.58), 1.71 (95% CI 1.35, 2.17) and 2.79 (95% CI 1.98, 3.94) compared with ever-pregnant women with no losses, respectively. Likewise, pregnancy loss remained a significant risk factor after adjustment for gestational diabetes (ESM Table 3). Women with 1, 2 and ≥ 3 pregnancy losses had an OR for type 2 diabetes of 1.14 (95%CI 1.10, 1.19), 1.32 (95% CI 1.21, 1.43) and 1.53 (95% CI 1.36, 1.73), respectively.

In the predefined subgroups of women with an expected relatively low proportion of fetal aneuploidy or a high probability of an immunological background, we found that all groups had an increased risk of developing type 2 diabetes (Table 3). Women with recurrent pregnancy loss (≥3 consecutive pregnancy losses) had an OR of type 2 diabetes of 1.65 (95% CI 1.44, 1.90). Women with secondary recurrent pregnancy loss after a firstborn boy had an OR for type 2 diabetes of 1.49 (95% CI 1.15, 1.93) and women with secondary recurrent pregnancy loss after a firstborn girl had an OR for type 2 diabetes of 1.28 (95% CI 0.95, 1.73). Women with recurrent pregnancy loss after a complicated delivery had an OR of 2.01 (95% CI 1.26, 3.20).

Discussion

In this nationwide study identifying 24,774 women with type 2 diabetes, we found that adverse outcomes in reproductive history were associated with a higher risk of type 2 diabetes later in life. This can be summarised into three main findings: (1) a strong and consistent association between pregnancy loss and type 2 diabetes, which increased with number of pregnancy losses indicating a dose–response association, not confounded by either obesity or gestational diabetes; (2) an increased risk of type 2 diabetes in women never achieving pregnancy; and (3) an increased risk of type 2 diabetes in

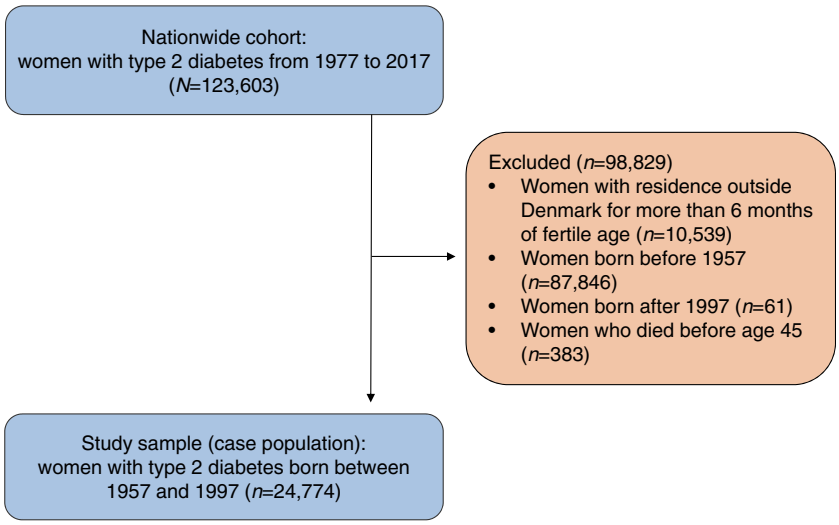

Fig. 1 Flowchart illustrating the selection of the study population

women with pregnancy losses with a high probability of euploid losses and losses with an immunological background.

To our knowledge, only a few previous studies have investigated the relationship between pregnancy loss and type 2 diabetes. In a recent prospective study based on self-reported data from 3546 women with type 2 diabetes, Horn et al. found an increased risk for later type 2 diabetes in women with pregnancy loss (HR 1.20 [95%CI 1.07, 1.34]) [27]. In addition, they found the increased risk of type 2 diabetes to be higher for women with ≥3 losses, and that late losses and stillbirths appeared to have stronger associations than early losses.

Our study confirms the findings by Horn et al., but in a large national setting not based on self-reported data, and provides additional data on women with consecutive pregnancy losses. Furthermore, owing to the nationwide sample, the present study had the power to investigate specific subgroups suspected to have a higher risk of later diabetes. Our subgroup definitions were based on a priori knowledge of groups with higher likelihood of euploid losses and, in addition, a higher likelihood of pregnancy losses with an immunological background. As expected, all subgroups except secondary recurrent pregnancy loss after a firstborn girl showed increased odds for type 2 diabetes. The association between these predefined groups and type 2 diabetes supports the theory that the association could be influenced by immunological factors, e.g. low-grade inflammation or metabolic disturbances with an immune component.

We cannot rule out that the psychological distress related to pregnancy loss can initiate lifestyle changes that increase BMI and thereby the risk of type 2 diabetes. We only had information about BMI for 12% of cases and 17% of controls as this

Table 1 Characteristics of cases (women with type 2 diabetes) and matched controls at index date

Variable	Cases (n = 24,774)	Controls (n = 247,740)	p value
Age at index, median (IQR)	40 (31–47)	40 (31–47)	0.965
Education, *n* (%)			1.000
No bachelor degree	18,531 (74.8)	185,310 (74.8)	
Bachelor degree	6243 (25.2)	62,430 (25.2)	
Gestational diabetes, *n* (%)	2135 (8.6)	1889 (0.8)	<0.001
Family history of diabetes, *n* (%)			
Mother with type 2 diabetes	2434 (9.8)	8929 (3.6)	<0.001
Father with type 2 diabetes	2452 (9.9)	11,384 (4.6)	<0.001
Siblings with type 2 diabetes	251 (1.0)	542 (0.2)	<0.001
Mother/father/sibling with type 2 diabetes	4661 (18.8)	20,009 (8.1)	<0.001
Obesity[a], *n* (%)	1662 (54.2)	6661 (15.8)	<0.001
Cardiovascular disease, *n* (%)	832 (3.4)	2646 (1.1)	<0.001
Hypertension, *n (%)*	2681 (10.8)	6495 (2.6)	<0.001

[a] Obesity was defined as pre-pregnancy BMI >30 kg/m^2. Information on BMI is available for 12% of the cases and 17% of the controls

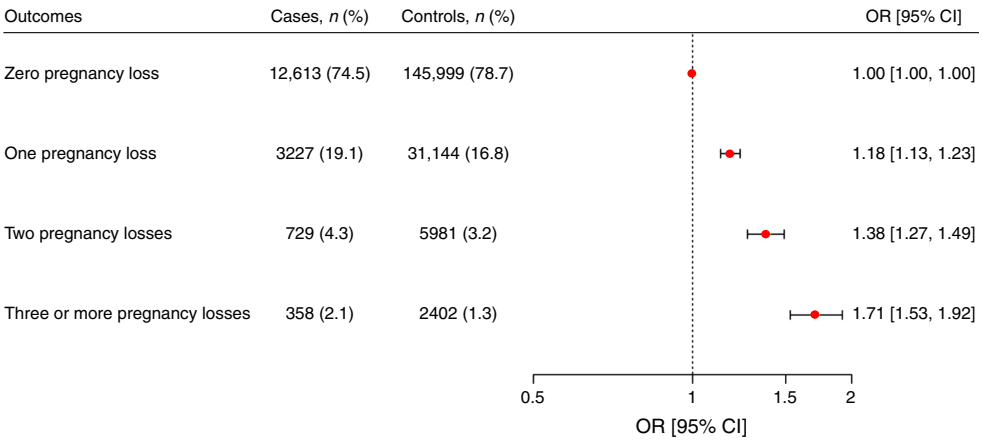

Fig. 2 ORs for developing type 2 diabetes according to number of pregnancy losses. Women with pregnancy losses were compared with ever-pregnant women with no losses

information was first recorded for pregnant women from 2004. However, our subgroup analysis in which we adjusted for obesity still showed a significant dose–response association between pregnancy loss and type 2 diabetes. Finally, the subgroup analysis indicated that the higher risk for type 2 diabetes in women with pregnancy loss cannot be explained by obesity alone.

Previously studies have found that gestational diabetes is a predictor for later development of type 2 diabetes. A recent study involving 4457 women with gestational diabetes found a risk for later type 2 diabetes of 23.1–27.2% [34]. The association between pregnancy loss and type 2 diabetes could therefore potentially be mediated through gestational diabetes. However, our subgroup analysis where we adjusted for gestational diabetes still showed a significant increased risk for type 2 diabetes in women with pregnancy losses. This indicates that pregnancy loss is an independent risk factor for type 2 diabetes.

Based on the high risk for type 2 diabetes in women with gestational diabetes, most guidelines recommend a close follow-up of women with gestational diabetes, mostly with HbA_{1c} after birth and then yearly [35]. Follow-up with HbA_{1c} is a simple and inexpensive method. A similar strategy could prove beneficial to women with ≥3 pregnancy losses. However, it is important to note that such a strategy should be monitored, and more research in pregnancy losses is crucial for a more targeted screening.

The association between pregnancy loss and type 2 diabetes could principally be due to a shared immunological and/or metabolic aetiology. Perhaps the same genetic background could predispose to an increased risk for both pregnancy losses and type 2 diabetes. In addition, pregnancy loss could initiate an immunological cascade that could lead to later type 2 diabetes. It is also possible that prediabetic metabolic conditions present before the diagnosis of diabetes could influence the association. Only a few smaller studies have investigated glucose metabolism in women with recurrent pregnancy loss. Two studies including a total of 124 women with recurrent pregnancy loss found a greater degree of insulin resistance in these women compared with control participants [36, 37]. Additionally, abnormal oral glucose tolerance was seen more frequently in women with recurrent pregnancy loss compared with control participants [38, 39]. Further research is needed to clarify the causation and possible mediation.

We found no previous study demonstrating an association between never achieving pregnancy and type 2 diabetes. These results should be interpreted with caution as the group encompasses women who have actively decided not to have children, women with chronic diseases making pregnancy impossible and finally women with unexplained infertility. A previous study on risk factors for diabetes failed to find an association between diabetes and infertility [40]; nevertheless, the robust association observed in the present study calls for further studies.

Table 2 Prevalence and ORs of pregnancy losses in the subgroup analysis for women with information about BMI with adjustment for obesity (BMI >30 kg/m^2)

	Cases (n = 3064)	Controls (n = 42,276)	OR (95% CI)	Adjusted OR (95% CI)	p value (adjusted OR)
0 pregnancy loss	2201 (71.8)	33,554 (79.4)	1	1	–
1 pregnancy loss	639 (20.9)	6954 (16.4)	1.42 (1.28, 1.58)	1.40 (1.25, 1.58)	<0.001
2 pregnancy losses	146 (4.8)	1268 (3.0)	1.74 (1.41, 2.16)	1.71 (1.35, 2.17)	<0.001
≥ 3 pregnancy losses	78 (2.5)	500 (1.2)	2.84 (2.09, 3.87)	2.79 (1.98, 3.94)	<0.001

Data are n (%)

Table 3 Prevalence and ORs of predefined types of pregnancy losses among ever-pregnant cases (women with type 2 diabetes) and ever-pregnant controls

	Cases (n = 16,927)	Controls (n = 185,526)	OR	95% CI	p value
≥3 pregnancy losses before age 30	177 (1.1)	1036 (0.6)	1.90	1.61, 2.24	<0.001
Recurrent pregnancy loss	238 (1.4)	1571 (0.9)	1.65	1.44, 1.90	<0.001
Primary recurrent pregnancy loss	127 (0.8)	727 (0.4)	1.96	1.61, 2.38	<0.001
Secondary recurrent pregnancy loss	111 (0.7)	844 (0.5)	1.40	1.14, 1.71	0.00119
≥1 live birth of a boy followed by recurrent pregnancy loss	67 (0.4)	486 (0.3)	1.49	1.15, 1.93	0.00267
≥1 live birth of a girl followed by recurrent pregnancy loss	49 (0.3)	401 (0.2)	1.28	0.95, 1.73	0.104
≥1 complicated delivery[a] followed by recurrent pregnancy loss	22 (0.1)	118 (0.06)	2.01	1.26, 3.20	0.00341
≥2 pregnancy losses in second trimester	30 (0.2)	232 (0.1)	1.54	1.04, 2.27	0.0308
≥1 stillbirth	270 (1.6)	1534 (0.8)	1.94	1.69, 2.21	<0.001

Data are n (%)

Predefined types of pregnancy losses were compared with ever-pregnant women with all other pregnancy outcomes

[a] Pregnancy complicated by preeclampsia, intrauterine growth restriction, preterm birth or placental abruption

While the epidemiological approach has limitations as correlation does not necessarily equate to causation, this nationwide case–control study has several strengths. Most importantly, the present study covers a complete national sample of women with type 2 diabetes and registered reproductive history, and is the first register-based study to explore the association between pregnancy loss and type 2 diabetes of a size by far exceeding previous cohorts [27, 28]. Previous studies investigating the association between type 2 diabetes and pregnancy loss have mainly been based on self-reported data [27, 28], and the cohort of women in the study by Horn et al. consisted mostly of well-educated women. The register-based approach is optimal to explore long-term associations because it is not limited by recall or selection bias, ensuring a high degree of external validity. The validity of the national Danish registers is generally high and the diagnoses of pregnancy loss and diabetes are validated to be of sufficient quality for epidemiologic research [41, 42].

A limitation of the study is that not all early pregnancy losses are handled in the hospital, but rather by gynaecological practitioners or at home, and therefore not registered. Very early pregnancy losses only detected by a positive pregnancy test (biochemical pregnancy losses) and pregnancy losses prior to approximately 6 gestational weeks are therefore often not registered. However, when matching with a control group the bias is reduced as the registration procedure is similar in cases and controls.

The significant differences in baseline characteristics between cases and controls (Table 1) are expected when comparing women with type 2 diabetes with women without diabetes and we have thus not adjusted the analysis for these variables as they are considered a consequence of the disease rather than confounders.

In conclusion, we found a significant and consistent association between pregnancy loss and later type 2 diabetes that increased with increasing number of losses. Thus, pregnancy loss and recurrent pregnancy loss seem to constitute indicators for later type 2 diabetes. The association was strongest in women with a high likelihood of euploid pregnancy losses and an immunological aetiology behind their losses. Whether metabolic conditions at the time of pregnancy loss explain the association with type 2 diabetes or the association is caused by a shared aetiology need to be explored in future studies.

Data availability The datasets from this study are not publicly available due to pseudo-anonymised data.

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Author's relationships and activities AMK has received speaker's fees from Merck Denmark A/S. HSN has served on the scientific advisory board for Ferring Pharmaceuticals and received speaker's fees from Ferring Pharmaceuticals, Merck Denmark A/S and Ibsa Nordic. FKK has served on scientific advisory panels and/or been part of speakers bureaus for, served as a consultant to and/or received research support from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Carmot Therapeutics, Eli Lilly, Gubra, MedImmune, MSD/Merck, Mundipharma, Norgine, Novo Nordisk, Sanofi and Zealand Pharma. PE, APM, SR, DW and ØL declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement The study was conceptualised by ØL and HSN. All authors made contributions to study design, data interpretation and preparation of the manuscript. PE and APM performed the data programming and statistical analysis and vouch for the accuracy and completeness of the data and analyses. The corresponding author (PE) had full access to all the data in the study, takes responsibility for the accuracy of the analysis, had authority over manuscript preparation and the decision to submit for publication and is the guarantor of this work. All authors approved the final version to be published.

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