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Parity and risk of diabetes in a Danish nationwide birth cohort

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Abstract

Aims The purpose was to elucidate the association between parity and the incidence of diabetes using national register data.

Methods The study population consisted of all Danish women with a singleton delivery in 1982/1983 (n = 100 669), who subsequently had 74 966 deliveries. The included women were followed up via registries until the end of 2006 for subsequent deliveries, diagnosis of diabetes and death/emigration.

Results A total of 2021 cases (2.0%) were diagnosed with diabetes in connection with hospitalization or outpatient treatment during follow-up. Analyses were adjusted for fetal weight and duration of gestation, both at index pregnancy. Cox regression analysis with parity as a time-varying exposure, stratified in two age groups, showed an association between parity and risk of a diagnosis of diabetes. In women <33 years of age, parity 2, 3 and 4 + were associated with an increased risk of being diagnosed with diabetes compared with parity 1 [relative risks: 1.6 (95% confidence interval 1.1–2.3), 2.8 (1.8–4.3) and 2.5 (1.3–4.8), respectively]. Among women >33 years of age, parity 2 was associated with a significantly lower risk of diabetes diagnosis compared with parity 1, whereas parity 4 + was associated with a significantly higher risk of diabetes diagnosis compared with parity 1.

Conclusions The study shows that the risk of diabetes diagnosis increases with parity in young Danish women. This may support a causal association between diabetes and parity.

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Keywords cohort, diabetes, multiparity, parity, pregnancy

Abbreviations BMI, body mass index; CI, confidence interval; RR, relative risk

Introduction

The prevalence of diabetes is escalating worldwide, mainly due to an increase in Type 2 diabetes. Some risk factors are well known, including age, adiposity and gestational diabetes, whereas the relationship between parity and diabetes has been a matter of discussion for many years. Some investigations have found that parity, particularly five or more births, may be associated with a higher incidence of diabetes [1–6], whereas others have found no association [7–10]. Glucose homeostasis is altered during pregnancy. Peripheral insulin sensitivity is reduced due to the action of several diabetogenic hormones [11,12], and the increased need for insulin is met by expansion of the ß cell mass [13]. Whether this metabolic stress during pregnancy confers an increased risk of diabetes remains an unresolved question.

To investigate the association between parity and the subsequent risk of diabetes, we performed a population-based study on a cohort consisting of all Danish women giving birth to a live singleton in 1982 and 1983. We linked these data to hospital discharge data, birth registries and the Danish civil registry to obtain information about parity, diabetes, vital statistics and emigration status.

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Patients and methods

The cohort consisted of all Danish women giving birth to a live singleton in 1982 and 1983 (primiparous as well as multiparous; n = 101 039) and was identified from the National Birth Registry in which maternal age, parity, fetal weight, sex and gestational age have been registered for all births since 1973. The first pregnancy within the time interval 1982–1983 is henceforth referred to as the index pregnancy.

Participants were followed up until the end of 2006 via the Danish National Registry of Patients which registers all diagnoses associated with patients hospitalized since 1978 and all outpatient treatments since 1995, and via the Danish civil registration system, which registers date of death or emigration. The end-point was a first-time diagnosis of diabetes (Type 1 or 2), excluding gestational diabetes, registered in the Danish National Register of Patients. Subjects who did not reach the end-point were either censored upon death or emigration or at the end of follow-up. Parity was used as a time-dependent exposure value that could change over the course of observation. The women were followed in the National Birth Register, and all pregnancies after the index pregnancy resulting in birth (n = 74 966 deliveries) were recorded and the fetal weight and duration of gestation registered.

Participants were excluded if they were diagnosed at index pregnancy with diabetes (Type 1 or 2) or gestational diabetes, defined as a diagnosis of diabetes occurring during pregnancy or within 2 weeks after birth (n = 294). Moreover, participants with obviously incorrect data registrations were excluded (Fig. 1). The following data were interpreted as such and excluded: fetal weight less than 500 or more than 7000 g; number of previous deliveries exceeding 100; and maternal age less than 12 or more than 51 years. Gestational age below 22 weeks was considered an abortion and gestational age more than 45 weeks an incorrect registration (n = 328). A women could have one or more of the mentioned typographical errors. In total, we excluded 370 participants (0.4% of the population). The final study population consisted of 100 669 women.

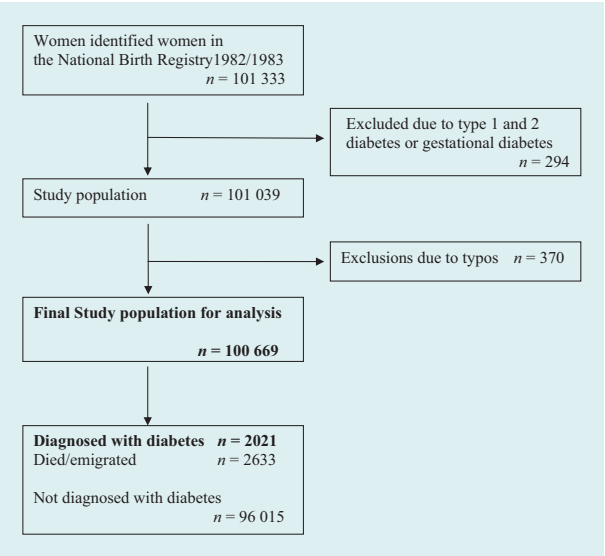

FIGURE 1 Flowchart of the study population.

Statistics

Cox proportional hazards regression was used to estimate the relative risk of being diagnosed with diabetes for women of the same age (age as time axis) but with different parities, assuming that the relative risk was constant across different ages (proportionality of hazards). Parity was included in the analysis as a time-dependent covariate, divided into 1, 2, 3 and 4 + , with primipara as reference, thus allowing women to move up in risk groups according to their changing parity.

Proportionality of hazards was assessed by visual inspection of plots of the Nelson–Aalen estimates of the log-cumulative hazard stratified according to parity. Stratification in two age groups was used to handle non-proportionality of hazards. In practice, this corresponded to independently analysing two cohorts; the first cohort consisting of women under a given cut-point age at index pregnancy who were censored at the cut-point age, and the second cohort consisting of women who had index pregnancy at the cut-point age or above plus those from the first cohort who had attained the cut-point age. The cut-point was chosen as the largest whole-year age for which the assumption of proportional hazards was accepted for the crude Cox regression model in both strata, according to the Schoenfeld test [14].

Potential confounding variables adjusted for in the analysis were fetal weight corrected for duration of gestation (Z-score) and the duration of gestation at the index pregnancy. Both variables entered the Cox regression analyses in the form of restricted cubic splines [15]. For each child, a Z-score was calculated as the deviation from the regression expressed in standard deviations at a given weight and duration of gestation. Negative Z-scores correspond to small-for-gestational-age infants and positive Z-scores to large-for-gestational-age infants.

Continuous data were summarized as means ± SD or median (interquartile range). Categorical variables were summarized as counts (%). All statistical tests were two-sided, and a P-value less than 5% was considered statistically significant. We used STATA version 10.1 for all analyses.

Results

A flowchart of the study is given in Fig. 1. Median maternal age at index pregnancy was 26.9 years (interquartile range 23.8–30.3). The 370 women excluded were younger than those included (median age 25.4 years; $P < 0.001$, Mann–Whitney U-test). The median length of follow-up was 23.9 years (interquartile range 23.4–24.5). Data from the index pregnancy in 1982 and 1983 are given in Table 1. In the study group of 100 669 women, 2021 participants (2.0%) were subsequently

diagnosed with diabetes (Table 2), and 2633 either died or emigrated (2.6%) during follow-up. At the index pregnancy, 45.4% of the women had no previous deliveries (n = 45 651). A tabulation of parity at end-point and diagnosis of diabetes is shown in Table 2. The median length of follow-up was 23.9 years for those not diagnosed with diabetes vs. 18.7 years for those diagnosed with diabetes.

Cox regression analysis of all women showed that parity was overall associated with the risk of diabetes diagnosis (P < 0.001). Plots of log-cumulative hazards by parity indicated violation of the assumption of proportional hazards (Fig. 2). The Cox regression analyses reported hereafter were therefore stratified in two age groups, with a cut-point of 33 years (with 220 and 1801 events of diabetes diagnosis, respectively).

The crude and adjusted relative risks (RR) of diabetes diagnosis are shown in Table 3. In women less than 33 years of age at end-point (diagnosed with diabetes, death or emigration), the risk of diabetes increased with parity in a dose-like pattern. Compared with primiparous women, the risk was significantly increased from parity 2 (RR = 1.61, 95% confidence interval 1.11–2.34) onwards. In the women older than 33 years of age, the pattern was different, as the risk of being diagnosed with diabetes was lower at parity 2 (RR = 0.74, 95% confidence interval 0.63–0.87), and higher at parity 4 + compared with the reference of parity 1. Cox regression analysis restricted to first-time pregnant women in 1982/1983 (n = 45 651) led to estimates of associations comparable to those based on the entire cohort (data not shown).

Table 1 Maternal age, parity, gestational age and fetal birth weight in the cohort of n = 100 669 women at the index pregnancy in 1982/1983

	Mean	SD	Median	Interquartile range
Maternal age (years)	27.3	4.74	26.9	(23.8–30.3)
Parity	1.78	0.91	2	(1–2)
Gestational duration (weeks)	39.66	1.83	40	(39–41)
Birth weight of girls (g)	3336.3	555.2	3350	(3030–3700)
Birth weight of boys (g)	3450.8	583.2	3500	(3130–3800)

Table 2 Number of women diagnosed with diabetes from 1982/1983 until the end of 2006 in relation to parity at end-point (end of follow-up, diagnosis of diabetes or death/emigration)

Parity	Population size	+ Diabetes
1	10 038	232 (2.31%)
2	48 411	755 (1.56%)
3	28 845	541 (1.88%)
4+	13 375	493 (3.69%)
Total	100 669	2021 (2.01%)

Discussion

Pregnancy, in particular the last trimester, is diabetogenic [11,16], and the number of deliveries may affect the risk of diabetes. The present study investigated the risk of being diagnosed with diabetes among multiparous women relative to primiparous women in a Danish birth cohort of more than 100 000 women. We found an association between parity and the risk of being diagnosed with diabetes during hospitalization or outpatient treatment. The data took into account age and adjusted for duration of pregnancy and relative fetal weight to account for the association between diabetes, elevated maternal glucose concentrations and an increased risk of large-for-gestational-age infants [17]. We found an approximate dose–response relationship among women less than 33 years of age, where increasing parity led to increasing risk of diabetes diagnosis compared with primiparous women. A different pattern was seen among women more than 33 years of age, in whom parity 2 was associated with a lower risk of diabetes diagnosis compared with primiparous women. The diagnosis of diabetes was drawn from the Danish National Register of Patients, which registers all patients in Denmark with diabetes registered during hospitalization and outpatient treatment. A previous study found a high validity of the diagnosis of Type 1 diabetes in this register [18]. The validity for uncomplicated Type 2 diabetes is presumably lower, since it is often diagnosed and treated in primary care and may not be registered in national databases. Although such misregistration may induce a degree of bias, our results indicate an association between parity and diabetes among younger women.

These results are in line with some other studies. Kritz-Silverstein reported that the risk of diabetes increases with increasing parity many years after childbearing [3]. An inverse association between parity and the age at diagnosis of diabetes was shown in a retrospective study among people with diabetes [4]. Two other studies [6,19] have found that the occurrence of

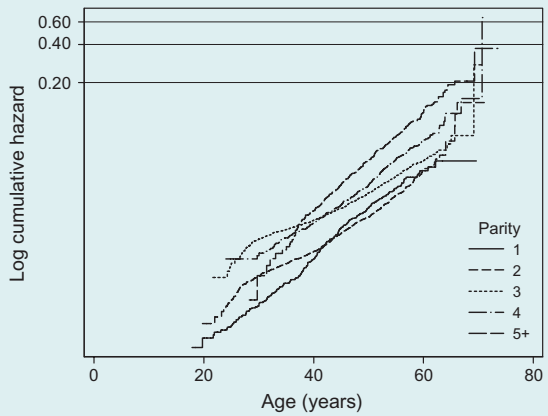

FIGURE 2 Nelson–Aalen estimates of log-cumulative hazards of diabetes as a function of maternal age for the different parities.

Table 3 Relative risks (RR) of diabetes associated with different parities, with parity 1 as a reference, in women less than and above 33 years of age at end-point

Parity	Events/person-years at risk	RR (crude)	95% CI	*P*-value	RR (adj)	95% CI	*P*-value
< 33 years							
1	43/200 301	1	—	—	1	—	—
2	109/304 314	1.74	(1.20–2.52)	0.003	1.61	(1.11–2.34)	0.01
3	56/84 160	3.32	(2.18–5.08)	<0.001	2.78	(1.82–4.25)	<0.001
4+	12/19 554	3.12	(1.61–6.04)	0.001	2.46	(1.27–4.78)	0.008
≥ 33 years							
1	189/186 030	1	—	—	1	—	—
2	646/864 843	0.74	(0.63–0.88)	<0.001	0.74	(0.63–0.87)	<0.001
3	486/498 569	0.91	(0.77–1.07)	0.25	0.87	(0.73–1.02)	0.09
4+	480/217 568	1.82	(1.53–2.15)	<0.001	1.64	(1.38–1.94)	<0.001

Definitions: adj, corrected for fetal weight (Z-score) and duration of gestation at index pregnancy; CI, confidence interval; and parity, parity at end-point (e.g. diagnosis of diabetes, death/emigration or at end of follow-up).

diabetes was independently associated with parity after adjustment for various risk factors. In contrast, other studies have found no association between parity and diabetes after adjusting for age and body mass index (BMI) [7–10]. These studies have a smaller study population than in our study [8–10], use simple grouping into parous and nulliparous women [9], use retrospective/cross-sectional design [8–10], have different ethnic groups [10] or have a shorter period of follow-up after birth [7,8]. In the Nurses' Health Study [7], which included 113 606 women, an association between diabetes and parity disappeared after controlling for age, BMI and other risk factors. In that study, the population was older (enrollment at age 30–55 years, median age in the forties) and the cohort was followed for a shorter period (12 years) than in the present study. We found that a parity of 2 was associated with a significantly lower risk of diabetes diagnosis than parity of 1 among women older than 33 years of age. In the Nurses' Health Study, a similar but non-significant trend was seen [7]. Socio-economic confounding may explain this finding; an alternative explanation is reduced fertility among primiparous women, which may be explained by conditions associated with an increased risk of diabetes, such as the polycystic ovarian syndrome [20].

Possible biological explanations for an association between parity and risk of diabetes, as was seen for younger women in the present study, could be a persistently increased insulin resistance in the peripheral tissue, with progressive aggravation in each pregnancy. In pregnancy, gestational hormones such as placental growth hormone, placental lactogen and circulating insulin-like growth factor-I promote insulin resistance and pancreatic ß cell proliferation. The ß cell mass expands in response to pregnancy [13], and as pregnancy progresses the insulin secretion must increase 1.5-fold in order to maintain maternal euglycaemia [11,16,21] This extra demand during pregnancy could exhaust the ß cells, resulting in a permanent derangement of insulin secretion.

Strengths of the present study include the completeness of data and avoidance of selection bias because of the nationwide nature of the study. The population in Denmark is relatively homogeneous (>90% Caucasian), and all citizens have free access to health services on equal terms. We excluded participants with obviously incorrect data, and these cases constituted only 0.4% of the total population. They are therefore unlikely to have had a significant impact on the conclusions. Information regarding demographic data, parity and birth weight in National Birth Register is considered valid, as is validity of Type 1 diabetes in the Danish National Register of Patients [18].

The study also has several weaknesses. The study design enabled us to examine the association between parity and risk of diabetes diagnosis in connection with hospitalization and outpatient treatment. While this exposure may be viewed as a proxy for general occurrence of diabetes, there is a risk of differential misclassification, where older women with many children are more likely to be diagnosed with diabetes than younger women with few children. It is therefore possible that a patient- or doctor-related bias in diagnosing diabetes may influence the observed association between the risk of a diagnosis of diabetes and parity. Likewise, diagnosis of Type 2 diabetes was incompletely registered. This may partly explain the observed association. Another limitation is the lack of socio-economic data and BMI data. Confounding from these known risk factors [22,23] for diabetes is also a possible explanation for the observed association. However, the association between parity and BMI is not unequivocal, and several long-term studies on BMI did not find a significant association between parity and BMI [3,24,25]. Finally, the present study compared multiparous women with primiparous women; another arguably important research question would be to compare parous women with nulliparous women.

In conclusion, we found that the risk of being diagnosed with diabetes during hospitalization or outpatient treatment increased from 2.5 times after four or more deliveries compared with primiparous women. This indicates an association between parity and risk of diabetes. The observed association was stronger for women under 33 years of age, indicating that parity accelerates the onset of later diabetes. Women above

33 years of age with only one child had a significantly greater risk of being diagnosed with diabetes compared with women with two children, an observation which may be explained by factors associated with subfertility.

Competing interests

Nothing to declare.

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