The Influence of Pregnancy on IDDM Complications

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OBJECTIVE — Although pregnancy has been associated with an increased progression of certain insulin-dependent diabetes mellitus (IDDM) complications, particularly retinopathy, both the short- and long-term relationships between pregnancy and both neuropathy and macrovascular disease are poorly documented. This study was conducted to comprehensively examine the influence of pregnancy on the development and progression of IDDM complications.

RESEARCH DESIGN AND METHODS — Using the Pittsburgh Epidemiology of Diabetes Complications Study population (childhood-onset IDDM), two nested, pair-matched case-control studies were conducted. Women who had completed at least one successful pregnancy (n = 80) were matched to women with no history of pregnancy by age, duration of IDDM, race, and marital history. The first nested study (study 1) compared the prevalences of five IDDM complications between case and control groups. The second nested study (study 2) compared the incidences of the same five complications over an approximate 2-year interval during which the case subjects (n = 30) completed a successful pregnancy.

RESULTS — There were no significant differences in the prevalence rates of coronary heart disease, neuropathy, proliferative retinopathy, lower extremity arterial disease, and overt nephropathy by case-control status, while parity did not predict any complication in multiple logistic analysis (study 1). In study 2, there were small but nonsignificant differences in incidence rates of overt nephropathy and lower extremity arterial disease between the groups, whereas case subjects had almost 3 times the incidence rate of proliferative retinopathy (P = 0.58) and 10 times the incidence rate of neuropathy ($P < 0.001$) as did other matched control subjects. In multivariate analysis, parity predicted neuropathy incidence but did not predict the incidence of any other complication, including proliferative retinopathy.

CONCLUSIONS — Women with IDDM who experience a pregnancy may not be at an increased risk of diabetes complications later in life. However, in the short term, pregnancy may accelerate the development of some complications, such as neuropathy.

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CI, confidence interval; EDC, Epidemiology of Diabetes Complications; IDDM, insulin-dependent diabetes mellitus.

The long-term effect of pregnancy on maternal health is a serious consideration for women with insulin-dependent diabetes mellitus (IDDM) who are contemplating childbirth. Pregnancy superimposes hormonal and circulatory changes on a woman who already suffers from a disease characterized by circulatory and metabolic dysfunction.

In the short term, pregnancy has been associated with an increased incidence of complications (1–14), in particular nephropathy (1–5) and retinopathy (8–14). However, the relationship between pregnancy and both neuropathy and macrovascular disease is still poorly documented, partly because these complications are rare among women of childbearing age. Furthermore, the long-term effect of pregnancy on the development of complications is unclear. The current study examines the influence of pregnancy on the short-term incidence and the longer-term prevalence of complications in a cohort of IDDM subjects.

RESEARCH DESIGN AND METHODS

— This study is based on the Epidemiology of Diabetes Complications (EDC) study population, which has been extensively described (15,16). The EDC study is a 10-year prospective cohort study in which the participants were initially examined in 1986–1988 (baseline) and every 2 years thereafter. Data from the first three cycles of examinations are used in this report (i.e., baseline, 2-year, and 4-year follow-up). The present report comprises two nested, pair-matched case-control studies. The first study examined the long-term prevalence of complications among parous women. All EDC participants who by the end of the 4-year examination (1990–1992) reported at least one successful pregnancy (resulting in a liveborn infant) were chosen as case subjects (with the exception of one mother of twins). Control subjects were still nulligravida at 4-year follow-up (six women with a known history of abortion, miscarriage, or stillbirth

were excluded). Case subjects and control subjects were matched for duration of diabetes within 12 months, age within 30 months, race, and marital history (ever been married versus never been married). Eighty pairs of women were matched according to these criteria and formed the population for the first nested study.

The second nested study examined the short-term incidence of complications among parous women. Subjects were the subset of cases from the first nested study who experienced a pregnancy between two consecutive biennial EDC clinic examinations and their respective control subjects. Of the 80 case subjects in the first population, 30 had experienced a pregnancy between biennial EDC examinations. These women and their same matched control subjects from the first study formed the second nested study population.

For the first nested study, the prevalence of each IDDM complication was compared between the case and control groups based on data from the cycle of examinations at which a pregnancy was first reported by the case subject. For the second nested study, the incidence of each complication was compared using data from the EDC examinations before and immediately after each pregnancy for each case subject, with comparative data for control subjects being taken from the same pair of examinations. The mean ± SD time intervals between the examinations immediately before and directly after each pregnancy were 29.3 ± 4.3 months for case subjects and 26.9 ± 4.9 months for control subjects. In the case group, the mean (± SD) time interval between delivery and the postpartum examination was 11.8 ± 7.7 months.

The complication end points were measured and defined as follows: Overt nephropathy was defined on the basis of: *1*) renal failure; 2) increased albumin excretion rate (>200 μg/min in at least two of the three timed urine samples, i.e., 24-h, overnight, and 4-h clinic sample); or 3) a serum creatinine level >180 μmol/l. Cases of nephropathy due to nondiabetic conditions were excluded from analysis. Albumin was measured by immunonephelometry (17).

Neuropathy

Distal symmetrical polyneuropathy was considered to be present if in the opinion of the examining physician after a clinical examination utilizing the Diabetes Control and Complications Trial protocol (18), at least two of three criteria were present and not due to a nondiabetic condition. Symptoms consistent with distal symmetrical polyneuropathy, decreased or absent tendon reflexes, and signs of sensory loss (vibratory sensation, light touch, and pin prick).

Retinopathy

Stereo fundus photographs of fields 1, 2, and 4 were taken with a Zeiss camera and read by the Fundus Photography Reading Center at the University of Wisconsin in Madison. Modified Airlie House System grades (19) were assigned to one of four categories: no retinopathy (grade 10 in both eyes); early background retinopathy (higher grade 20 or 30 in either eye); advanced background retinopathy (higher grade 40 or 50 in either eye); and proliferative retinopathy (grade 60 or above in either eye). A history of laser therapy was coded as proliferative retinopathy if the history suggested that the therapy was for proliferative retinopathy.

Peripheral vascular disease

An ankle-arm blood pressure ratio <0.8 at rest or a history of amputation for peripheral vascular disease were both considered definite indications of the presence of peripheral vascular disease (20).

Cardiovascular disease

Cardiovascular disease was defined on the basis of: *1*) a history of myocardial infarction (or evidence of a past myocardial infarction on the basis of electrocardiographic findings such as pathological Q waves at the time of examination) that conformed to the Community Cardiovascular Surveillance Program criteria (21) on review of hospital records; 2) diagnosis of angina by the examining clinic physician; 3) documented coronary artery disease by angiography (≥50% stenosis); or 4) a history of stroke, again confirmed by review of hospital records.

Statistical analysis

Statistical analyses were performed with BMDP software. McNemar's test of symmetry for matched pairs was used to evaluate the discordant pairs of case subjects and control subjects with positive complication status. This test resulted in odds ratios that do not correspond to basic arithmetic ratios but reflect the greater power afforded by a matched-pair study. To calculate the incidence of complications in study 2 for each complication, subjects (whether case or control) with that complication were excluded and the number found to have developed that complication at follow-up examination was divided into the number at risk from previous examinations.

Multiple regression analyses were also performed using BMDP statistical software. The dependent variables were the five complication end points retinopathy, neuropathy, nephropathy, peripheral vascular disease, and cardiovascular disease. The independent variables were chosen based on their univariate correlation with the dependent variable. Two predictor variables, albumin excretion rate and triglycerides, were not normally distributed and thus were transformed to a logarithmic scale before being entered into the models. Stepwise logistic regression was used to determine the independent predictors related to the criterion variable.

RESULTS — Table 1 describes the basic demographic characteristics of the study population. These did not differ by case-control status. In addition, there were no significant differences (data not shown) in daily insulin dose, weight, height, physical activity (as measured by daily distance walked), income level, fibrinogen, triglycerides, high- or low-

Table 1—*Study 1 (prevalence) basic characteristics: the EDC Pregnancy Study*

	Case subjects	Control subjects
n	80	80
Mean duration (years)	20.7	20.2
Mean age (years)	29.9	29.1
Mean HbA_1 (%)	10.0	10.3
Mean body mass index	23.9	24.9
Ever smoked (%)	36.0	29.0
Hypertension (%)	14.7	14.7
College education (%)	52.5	66.3
Mean AER (log)	3.5	3.9

All differences between case and control subjects are nonsignificant. Values for albumin excretion rate (AER) are medians (of three samples) μg/min (log transformed).

Table 2—*Study 1 prevalence of complications by case-control status: the Pittsburgh EDC Pregnancy Study*

	Case subjects	Control subjects	Odds Ratio (95% CI)
Coronary heart disease	5	4	1.34 (0,19, 11.16)
Lower extremity arterial	10	17	0.55 (0.15, 1.78)
Neuropathy	47	47	1.00 (0.48, 2.08)
Overt nephropathy	39	51	0.57 (0.25, 1.29)
Proliferative retinopathy	35	36	0.94 (0.46, 1.95)

Data are percentages. Parity did not predict any complication in multiple logistic analysis.

density lipoprotein cholesterol, and systolic (or diastolic) blood pressure between case subjects and control subjects. A paired *t* test *P* value of 0.07, however, suggested a marginally higher mean albumin excretion rate in the control group.

The mean number of daily insulin injections was higher ($P = 0.07$) in the control group (1.9) than in the case group (1.7), while 6.3% of the case subjects compared with 17% of the control subjects ($P = 0.05$) were on a program of either a minimum of three insulin injections per day or an insulin pump.

Table 2 presents the prevalence of complications in both case subjects and control subjects and associated odds ratios for matched pairs. Essentially no case-control differences were seen (all *P* values were nonsignificant while the 95% confidence intervals [CIs] included unity). Parity did not predict any complication in multiple logistic analysis (data not shown).

The demographic characteristics for the second nested study population are found in Table 3. Again, no significant differences were found between case subjects and control subjects. The incidence rates of the five complications are shown in Table 4 for the approximate 2-year interval between examinations. No incidence of coronary heart disease was seen. For overt nephropathy and lower extremity arterial disease, there were small but nonsignificant differences in incidence between case subjects and control subjects. Although the difference in incidence for proliferative retinopathy was greater (case subjects were almost three times as likely as control subjects to develop proliferative retinopathy, 25.0% vs. 9.1%), it was far from significant, at $P = 0.58$. However, case subjects were nearly 10 times as likely as control subjects to develop neuropathy (41.7% vs. 4.8%, $P < 0.001$). The 95% CIs for the pair-matched odds ratios confirm the association with neuropathy. Additionally, in multivariate analysis, parity predicted neuropathy incidence but did not predict the incidence of any other complication, including proliferative retinopathy (data not shown).

CONCLUSIONS — These results suggest that women with diabetes who experience a pregnancy may not be at an increased risk of diabetes complications later in life. No significant differences were found between the case subjects and the control subjects. Parity, therefore, does not appear to be a risk factor in the progression of diabetes complications in women with IDDM.

The only other comprehensive study of multiple complications we have identified was conducted by Carstensen et al. (22), who compared the prevalence of complications in 22 pairs of women with IDDM. These authors also concluded that prior pregnancy does not affect the prevalence of retinopathy, nephropathy, or neuropathy. This general conclusion is strengthened by the fact that the current study and Carstensen's differed significantly in inclusion criteria (Carstensen and associates excluded subjects using oral contraception and those overweight or having proliferative retinopathy), design (the current study matched on marital history as well as age and duration), and methodology for determining nephropathy and retinopathy.

The second component of this investigation, involving the subset of women who experienced a pregnancy between examinations, studied incidence data. The limited sample size (30 pairs), although large compared with previous studies, does compromise the power to

Table 3—*Study 2 (incidence) basic characteristics: the Pittsburgh EDC Pregnancy Study*

	Case subjects	Control subjects
n	30	30
Mean duration (years)	19.1	20.1
Mean age (years)	27.6	28.4
Mean HbA_1 (%)	10.2	10.4
Mean body mass index	24.9	24.1
Ever smoked (%)	33.3	23.3
Hypertension (%)	13.3	16.7
College education (%)	66.7	70.0

All differences between case and control subjects are nonsignificant.

Table 4—*Study 2 2-year incidence of complications by case-control status: the Pittsburgh EDC Pregnancy Study*

	Case subjects	Control subjects	OR	(95% CI)
Lower extremity arterial	3.8	7.7	0.50	(0, 15.26)
Neuropathy	41.7	4.8	10.00	(1.10, >100)
Overt nephropathy	6.7	10.5	0.50	(0, 15.26)
Proliferative retinopathy	25.0	9.1	1.60	(0.41, 6.89)

Data are percentages. Parity is the only predictor for neuropathy, but it did not add to the prediction of proliferative retinopathy in multiple logistic analysis.

detect meaningful differences in incidence between case subjects and control subjects. For example, with an α-level of 0.05 and a power of 80%, only five matched pairs of women would be required to detect differences by case-control status for neuropathy, while 34 matched pairs would be needed for proliferative retinopathy (given the observed incidences). For cardiovascular disease, peripheral vascular disease, and nephropathy, sample sizes well beyond the scope of this subset study would be required. This study showed an increased incidence of neuropathy and a nonsignificant yet threefold increase in the incidence of proliferative retinopathy which were the only two complications with appropriate power. It is possible that with a larger sample size, significant differences in the incidence of other complications might be detected.

The marked increased incidence of neuropathy in the pregnancy group (study 2) led to a consideration that these incident neuropathy cases reflected postpartum rather than diabetic neuropathy. However, this is unlikely to be the case. Many of the case subjects were examined more than 1 year after the pregnancy, and the intervals between the pregnancy and the subsequent EDC examination were comparable for both incident case subjects and control subjects. More importantly, the distributions of signs and symptoms of neuropathy were the same as for non–pregnancy-associated neuropathy, and there was no pattern suggestive of postpartum femoral neuropathy or carpal tunnel syndrome.

The incidence of proliferative retinopathy during pregnancy (or the influence of pregnancy on the incidence of proliferative retinopathy) in the current study is in close agreement to that found by two other studies utilizing similar definitions and criteria to characterize the complication (10,12). In contrast, two studies reporting a considerably lower incidence of proliferative retinopathy in association with pregnancy have included women with a much shorter duration of IDDM and a different protocol for establishing (and scoring) the diagnosis and severity of the disorder (13,14).

The prevalence of complications in this study population is comparable to rates reported by other investigators for women with a 20-year duration of IDDM. Borch-Johnsen et al. (23) found that nephropathy occurs in ~40% of patients with IDDM, which corresponds well to the 39% of case subjects and 51% of control subjects who experienced nephropathy in this study. For proliferative retinopathy, Klein et al. (24) found a 22% prevalence among women with a 15-year duration of IDDM; while in the overall EDC population (15), a prevalence of two-thirds for women with a 30-year duration of IDDM is noted.

In this study population, although there was no significant difference in the number of insulin injections taken per day by case subjects and control subjects, there was a trend toward significance. Compared with 6.3% of the case subjects, 17.5% of control subjects were on a program of strict glycemic control involving an insulin pump or at least three insulin injections per day. This almost threefold difference presents a possible bias in that the control group may have experienced fewer complications or slower progression of complications because of better glycemic control. However, baseline glycemic control (as measured by HbA_1) did not differ by case-control status, and the results did not change when HbA_1 was incorporated into the multivariate models.

When the prevalences of the five complication end points in the first nested study were stratified by parity, there did not appear to be a dose effect; i.e., the risk of complications did not increase with the number of pregnancies experienced. However, the power after stratification by parity is insufficient to fully examine this issue.

A concern with all prevalence studies is the inability to establish the temporal relationship of exposure (in this case pregnancy) and outcome (complications), and to exclude bias. Thus, although all the case subjects had experienced pregnancy and most had also developed IDDM complications, it cannot be assumed that the pregnancies preceded the development of complications. Furthermore, despite the fact that the control subjects were nulligravida and most had developed some IDDM complications, it remains possible that these complications may have affected their decisions not to become pregnant. On balance, we believe that these concerns, although real, do not detract from the conclusion that pregnancy has little effect on eventual complication status. However, the issue of short-term risk and a temporal association can be examined in the second (incident) study and suggests that women experiencing a pregnancy may have a 10-fold increased risk of neuropathy (41.7%) compared with their matched control subjects (4.8%). Thus, pregnancy seems to have accelerated the

progression of this complication. Logistic regression analysis demonstrated that only parity was strongly associated with neuropathy incidence in this subset of the population. However, when the entire study population was considered, no association with parity was found, suggesting that while neuropathy progresses more rapidly to the level of clinical detection in susceptible patients during pregnancy, it does not lead to a greater overall frequency of neuropathy than would otherwise occur.

These results suggest that women with IDDM who experience a pregnancy are unlikely to be at an increased risk of diabetes complications later in life. While in the short-term pregnancy may accelerate the development of some complications, such as neuropathy and proliferative retinopathy (based on other studies), in the long term it is not associated with a poorer prognosis.

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