Factors Associated With Preterm Delivery in Women With Type 1 Diabetes

A cohort study

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OBJECTIVE — The reported rate of preterm delivery in women with type 1 diabetes ranges from 22 to 45%, but the reasons are unclear. The purpose of this study was to identify factors associated with preterm delivery in these women.

RESEARCH DESIGN AND METHODS — We studied the influence of maternal and diabetes-related factors on the occurrence of preterm delivery in 168 single pregnancies occurring in 127 women with type 1 diabetes. Women with spontaneous or indicated preterm delivery were compared with those who delivered after 37 weeks of gestation using polytomous logistic regression.

RESULTS — The overall rate of preterm delivery was 24%, fivefold higher than the French prematurity rate in single pregnancy. Preterm delivery was spontaneous in 9% and indicated in 15%. $HbA_{1c} \geq 7\%$ at delivery was associated with spontaneous preterm delivery (odds ratio [OR] 5.3 [95% CI 1.1–26.8]). Nulliparity (12.0 [2.3–64.1]), progression of nephropathy (7.7 [1.3–46.9]), preeclampsia (12.0 [3.1–47.1]), and $HbA_{1c} \geq 7\%$ (7.5 [1.5–37.9]) at delivery were all associated with indicated preterm delivery. Preterm delivery was associated with significant neonatal morbidity as the risks for neonatal hypoglycemia and respiratory distress syndrome were increased by three- to sixfold compared with the reference group.

CONCLUSIONS — The rate of preterm delivery remains high in women with type 1 diabetes. Different factors were associated with spontaneous and indicated preterm delivery, respectively. Because poor glycemic control was a risk factor for both outcomes, part of preterm delivery might be preventable.

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Recent surveys have shown that perinatal complications are still increased in women with type 1 diabetes (1–4). Particularly, the rate of preterm delivery ranged from 22 to 45% in women with type 1 diabetes, i.e., increased by four- to eightfold over the frequency of preterm delivery in nondiabetic single pregnancies (5–10). Preterm delivery is either spontaneous or indicated for maternal or fetal reasons. The rate of both spontaneous and indicated preterm delivery is increased in women with type 1 diabetes. Spontaneous preterm delivery, due to preterm labor or premature rupture of the membranes, has been associated with poor glycemic control (5,11) and urogenital infections (5). Indicated preterm delivery has been primarily related to the increased occurrence of preeclampsia in women with type 1 diabetes (6,9).

However, in many previous studies, data on diabetes complications, preconception care, and glycemic control during pregnancy have not been systematically collected. The aim of the present study was to assess the factors that may be associated with spontaneous and indicated preterm delivery in a cohort of women with type 1 diabetes, all followed at the same institution according to a standardized protocol. A secondary objective was to determine whether risk factors for preterm delivery could be identified before or during early pregnancy and might lead to prevention.

RESEARCH DESIGN AND METHODS

— All women with type 1 diabetes and a single pregnancy who consecutively delivered after 22 weeks of gestation in the Department of Obstetrics and Gynecology, Cochin-Saint Vincent de Paul Hospital, between 1997 and 2002 were included in the study.

Women of child-bearing age were informed about the need for preconception care. Preconception care included assessment of diabetes complications, review of dietary habits, intensification of capillary blood glucose self-monitoring (before and 2 h after each of the three main meals), and optimization of insulin therapy. Insulin therapy was given by three to four daily injections or with continuous subcutaneous infusion using an external pump. Capillary blood glucose target values were <95 mg/dl (5.3 mmol/l) before meals and <120 mg/dl (6.7 mmol/l) 2 h postprandial. HbA_{1c} was measured by

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Abbreviations: LGA, large for gestational age; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; SGA, small for gestational age; UAE, urinary albumin excretion.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Main characteristics at enrollment and during pregnancy in the whole cohort (168 pregnancies in 127 women with type 1 diabetes)*

Parameters	Data
Maternal age (years)	30.4 ± 4.7
Ethnicity, caucasian	157 (94)
Social class, white collar	96 (57)
Marital status, married	161 (96)
Smoking	15 (9)
Nulliparous	97 (58)
Previous preterm delivery	17 (10)
BMI (kg/m^2)	23.0 ± 2.9
Duration of diabetes (years)	14.8 ± 7.7
Retinopathy	67 (42)
Nephropathy	18 (11)
Chronic hypertension	9 (6)
Preconception care	107 (65)
First trimester HbA_{1c} (%)	6.9 ± 1.1
HbA_{1c} at delivery (%)	6.2 ± 0.8
Progression of retinopathy	14 (10)
Progression of nephropathy	10 (7)
Preeclampsia	22 (13)
Urogenital infection	8 (10)
Polyhydramnios	35 (21)

Data are mean ± SD or *n* (%).

high-performance liquid chromatography (normal 4.3–5.5%) at enrollment and at delivery. A first trimester, HbA_{1c} <7% was used as a surrogate marker for efficient preconception care. During pregnancy, women were seen every other week at the diabetes clinic and spoke with a member of the team by phone as often as needed.

All women were followed monthly at the obstetric clinic and had three ultrasound scans during pregnancy at 12–14, 22–24, and 32–34 weeks of gestation according to French recommendations. Nonstress tests were performed twice weekly from 32 weeks until delivery. Polyhydramnios was defined as an amniotic fluid index >25 cm (12). Vaginal and urinary tract infections were systematically tracked. Urine specimens were analyzed monthly. Specimens from genital tract and urine were systematically analyzed during hospitalization for preterm labor or premature rupture of the membranes and at delivery. Vaginal infection was defined as a positive genital culture for group B streptococci, *Chlamydia trachomatis*, or Ureaplasma urealyticum. Urinary tract infection was defined as a colony-forming units of a uropathogen >10^5/ml.

Maternal baseline characteristics included age, ethnicity, marital status, social class, parity, smoking habit, previous preterm delivery, prepregnancy, and BMI. Two social classes, white collar and blue collar, were defined based on the usual lifetime occupation. Diabetes characteristics included duration of diabetes, retinopathy, nephropathy, and chronic hypertension. Retinopathy was classified as absent, mild nonproliferative, moderate nonproliferative, severe nonproliferative, or proliferative. Ophthalmological examination was performed during pregnancy each trimester in women without retinopathy and at least monthly in those with a preexisting retinopathy. Progression of retinopathy was defined as a higher stage at last evaluation than that at baseline. Nephropathy was classified on the basis of prepregnancy urinary albumin excretion (UAE) rate as absent (UAE <30 mg per 24 h), incipient (UAE rate 30–300 mg per 24 h), overt (UAE rate >300 mg per 24 h), or renal failure (creatinine clearance <90 ml per min). Progression of nephropathy was defined as a higher stage at last evaluation than that at baseline. Hypertension was defined as a systolic blood pressure level ≥140 mmHg or a diastolic blood pressure level ≥90 mmHg. Chronic hypertension was defined as hypertension that is present before pregnancy or that is diagnosed before the 20th week of gestation; gestational hypertension was defined as hypertension that is diagnosed after 20 weeks of gestation on two occasions at least 6 h apart in women with previously normal blood pressure. Preeclampsia was defined by gestational hypertension associated with proteinuria ≥300 mg per 24 h (13). In women with chronic hypertension, preeclampsia was diagnosed when proteinuria occurred after 20 weeks of gestation. In women with nephropathy, diagnosis of preeclampsia depended on a combination of worsening hypertension or proteinuria.

The obstetrical management for timing of delivery was guided by gestational age according to a standardized protocol. Women were generally delivered between 38 and 39 weeks of gestation. During labor and delivery, intravenous infusions of glucose and insulin were used with hourly blood glucose monitoring (with a target of 80–140 mg/dl). Before 34 weeks of gestation, fetal lung maturation with β-methasone (12 mg intramuscularly, two doses every 24 h) was systematically performed in women at risk of either spontaneous or indicated preterm delivery. Insulin therapy was adapted during the course. In women with preterm labor, 48-h intravenous tocolysis with either calcium channel blockers (nicardipine) or oxytocin antagonist (atosiban) was administered. In women with preterm premature rupture of the membranes, conservative management was decided in the absence of choriamnionitis. Tocolysis and 48-h adjunctive antibiotherapy with amoxicilline and netromicine were administered. In the indicated preterm delivery group, glucocorticoid before delivery was administered when possible, i.e., in the absence of maternal and/or fetal compromise requiring immediate delivery. After 34 weeks of gestation, prompt delivery was decided systematically in women with preterm premature rupture of the membranes. In the indicated preterm delivery group, the timing of delivery was decided upon by case-by-case benefit/risk ratio estimation.

The main analyzed outcome was the occurrence of preterm delivery, defined as delivery before 37 weeks of gestation. Gestational age at delivery was determined from the date of the last menstrual period confirmed by first-trimester ultrasonography. Other outcomes included birth weight and neonatal complications. Birth weight according to gestational age was used to define infants as small (SGA), appropriate, and large (LGA) for gestational age infants according to the French growth standard curves (14). Neonatal complications included admission to neonatal intensive care unit (NICU), hypoglycemia, respiratory distress syndrome (RDS), and intraventricular hemorrhage. Neonatal hypoglycemia was defined as the occurrence of a serum glucose level of <40 mg/dl (2.2 mmol/l) despite systematic prevention by the injection of glucagon (0.3 mg/kg) at birth. RDS was defined as the need for oxygen therapy or invasive ventilation for >24 h. All protocols were approved by the institutional ethics review board of Cochin Hospital, Rene Descartes University, and all the mothers gave their informed consent.

Because spontaneous and indicated preterm delivery are obviously different clinical situations, these groups were considered separately and compared with the reference group, i.e., women who deliv-

Table 2—*Factors associated with spontaneous and/or indicated preterm delivery*

	Spontaneous preterm delivery			Indicated preterm delivery		
	OR	95% CI	*P*	OR	95% CI	*P*
Age >35 vs. 25–35 years	1.9	0.4–8.2	0.41	0.8	0.2–3.3	0.73
Age <25 vs. 25–35 years	7.7	1.6–36.6	0.01	0.4	0.1–5.5	0.52
Ethnicity, caucasian	0.8	0.2–4.0	0.77			
Social class, white collar	2.6	0.8–8.1	0.11	1.4	0.6–3.2	0.39
Marital status, married	2.2	0.2–21.4	0.50			
Smoking	0.6	0.1–5.4	0.68	0.8	0.2–3.6	0.80
Nulliparous	1.5	0.5–4.6	0.44	4.9	1.6–14.7	0.005
Previous preterm delivery	2.2	0.6–8.1	0.25	0.8	0.2–4.1	0.81
BMI	1.0	0.8–1.2	0.80	0.9	0.8–1.1	0.53
Duration of diabetes	1.0	0.9–1.1	0.65	1.0	0.9–1.0	0.55
Retinopathy	0.7	0.2–2.3	0.58	1.6	0.7–3.7	0.31
Nephropathy	1.6	0.3–8.3	0.60	2.8	0.8–9.9	0.10
Chronic hypertension	2.1	0.2–20.7	0.52	6.3	1.7–23.1	0.006
Preconception care	0.5	0.2–1.4	0.18	1.3	0.5–3.6	0.55
Progression of retinopathy	1.4	0.2–12.1	0.78	4.1	1.2–14.0	0.03
Progression of nephropathy				6.6	1.7–25.6	0.006
First trimester HbA_{1c}	1.3	0.9–1.8	0.12	1.3	0.9–1.8	0.18
HbA_{1c} at delivery	2.0	1.2–3.3	0.01	1.8	1.1–3.1	0.03
Preeclampsia				18.9	7.0–51.5	<0.001
Urogenital infection	1.6	0.2–14.7	0.69	2.1	0.4–11.6	0.42
Polyhydramnios	6.2	1.8–21.7	0.004	1.2	0.4–3.6	0.73

Results of the univariate analysis are expressed as OR and its 95% CI vs. reference group (term delivery).

ered after 37 weeks of gestation using polytomous logistic regression. Multilevel modeling was performed to account for the clustering effect of women having several pregnancies. Factors that were associated with the dependent variable at $P < 0.20$ in the univariate analysis were entered into the multivariate model and eliminated using a backward procedure. Only variables associated with spontaneous or indicated preterm delivery ($P < 0.10$) were kept in the final model. Results are expressed using the exposure odds ratio (OR) and its 95% CI. Statistical analysis was performed with STATA software (release 7.0; Stata, College Station, TX).

RESULTS — A total of 168 consecutive single pregnancies occurring in 127 women with type 1 diabetes were included in the analysis. One hundred twenty-seven women delivered once, 34 twice, 6 three times, and 1 four times during the study period. Characteristics at enrollment and during pregnancy are shown in Table 1. Forty-one deliveries occurred between 32 and 37 weeks of gestation, thus the overall preterm delivery rate was 24%. Preterm delivery was spontaneous in 16 cases (9%) and indicated in 25 cases (15%). Gestational age at birth was similar in the spontaneous and indicated preterm delivery groups (35.3 ± 1.0 vs. 35.3 ± 1.1 weeks of gestation, $P = 0.58$).

The reasons for spontaneous preterm delivery were preterm labor in 3 cases and preterm premature rupture of the membranes in 13 cases. In the univariate analysis, there was no difference between spontaneous preterm delivery and reference groups regarding ethnicity, social class, marital status, smoking, prepregnancy, BMI, parity, the occurrence of previous preterm delivery, duration of diabetes, chronic hypertension, rate of preconception care, gestational age and HbA_{1c} at enrollment, the existence or progression of retinopathy or of nephropathy, and the prevalence of urogenital infection (Table 2). In the spontaneous preterm delivery group, maternal age was lower, HbA_{1c} at delivery was higher, and polyhydramnios was more frequent than in the reference group (Table 2). However, in the multivariate analysis, HbA_{1c} ≥7% at delivery was the only parameter that remained associated with spontaneous preterm delivery (Table 3). None of the parameters available at enrollment was associated with spontaneous preterm delivery.

The main reason for indicated preterm delivery was preeclampsia ($n = 14$, 56% of the cases). Other reasons were fetal growth restriction ($n = 1$), poor glycemic control ($n = 2$), congenital malformation ($n = 1$), macrosomia ($n = 2$), nonreassuring fetal heart rate ($n = 3$), acute polyhydramnios ($n = 1$), and acute fatty liver of pregnancy ($n = 1$). In women from the indicated preterm delivery group, nulliparity, chronic hypertension, progression of retinopathy and of nephropathy, and preeclampsia were more frequent, and HbA_{1c} at delivery was higher than in the reference group (Table 2). During pregnancy, progression of nephropathy, occurrence of preeclampsia, and HbA_{1c} ≥7% at delivery remained associated with indicated preterm delivery (Table 3). In the multivariate analysis, the only parameter available at enrollment that remained associated with indicated preterm delivery was nulliparity (Table 3).

Table 3—*Factors independently associated with spontaneous and indicated preterm delivery*

	Spontaneous preterm delivery			Indicated preterm delivery		
	OR	95% CI	*P*	OR	95% CI	*P*
Age >35 vs. 25–35 years	2.3	0.4–15.2	0.38	0.7	0.2–3.3	0.70
Age <25 vs. 25–35 years	5.2	0.8–32.8	0.08	0.7	0.1–10.3	0.77
Nulliparous	2.1	0.4–10.5	0.37	12.0	2.3–64.1	0.003
HbA_{1c} ≥7% at delivery	5.3	1.1–26.8	0.04	7.5	1.5–37.9	0.01
Progression of nephropathy				7.7	1.3–46.9	0.03
Preeclampsia				12.0	3.1–47.1	<0.001

Data are OR and its 95% CI vs. reference group. Final multivariate model included maternal age and variables associated with the outcome with $P < 0.05$. In this model, HbA_{1c} at delivery was dichotomous ≥7% vs. <7%.

Neonatal outcomes are reported in Table 4. Admission to NICU (OR 6.0 [95% CI 2.7–13.0], $P < 0.0001$), RDS (6.9 [2.6–18.3], $P < 0.0001$), and neonatal hypoglycemia (3.2 [1.5–6.7], $P = 0.003$) were significantly increased in premature infants. RDS was reported in 13 premature infants and 8 from the reference group. Four premature infants required >24 h of invasive ventilation. No intraventricular hemorrhage was reported. The frequency of neonatal complications was similar in the spontaneous and indicated preterm delivery groups. Although mean birth weight percentile was lower in the indicated compared with the spontaneous preterm delivery group (69 ± 25 vs. 86 ± 13, $P < 0.05$), the prevalence of SGA infants was not increased in the indicated preterm delivery group.

Table 4—*Neonatal outcomes*

	Spontaneous preterm delivery	Indicated preterm delivery	Term delivery
n	16	25	127
Gestational age (weeks)	35.3 ± 1.0	35.3 ± 1.1	37.9 ± 0.6
Birth weight percentile	86 ± 13	69 ± 25	76 ± 24
SGA	0	0	1
NICU	11 (69)	19 (76)	40 (31)
RDS	5 (31)	8 (32)	8 (6)
Hypoglycemia	8 (50)	12 (48)	29 (23)

Data are means ± SD or *n* (%).

CONCLUSIONS — Among the women who participated in the study, the rate of preterm delivery was 24%, which is consistent with rates of 22–45% reported in previous studies (5–10). All preterm deliveries occurred between 32 and 37 weeks of gestation; none occurred before 32 weeks of gestation. Nevertheless, preterm delivery was associated with significant neonatal morbidity since the risks for neonatal hypoglycemia, RDS, and admission to NICU were respectively threefold, sixfold, and sevenfold higher in the preterm delivery group compared with the reference group. No difference in the frequency of neonatal complications was observed between the spontaneous and the indicated preterm delivery group.

This study was intended to identify factors potentially associated with preterm delivery in women with type 1 diabetes. Indeed, reports describing the reasons for preterm delivery among women with type 1 diabetes are scarce. In a recent French multicentric survey of 435 pregnancies in women with pregestational diabetes, preterm delivery, which occurred in 38%, was of unknown origin in 39% of the cases (3).

In the present study, the rate of spontaneous preterm delivery was 9%, similar to the rates of 8 and 10% reported in two studies (6,10) but lower than the rates of 16 and 18% reported by others (5,9). The reasons leading to an increased rate of spontaneous preterm delivery in women with type 1 diabetes are imprecise. We found a significant association between HbA_{1c} ≥7% at delivery and spontaneous preterm delivery. This is in keeping with the association reported between poor glycemic control from midpregnancy onward and spontaneous preterm delivery (5,11). In our study, polyhydramnios and macrosomia were not associated with spontaneous preterm delivery. A higher rate of LGA infants would have been expected as glycemic control was poorer in the spontaneous preterm delivery group, but the difference in birth weight percentile for gestational age compared with the reference group was not significant (86 ± 13 vs. 76 ± 24, $P = 0.25$). At variance with a previous study (5), urogenital infections were not associated with spontaneous preterm delivery, but the rate of events was very low among our patients.

The rate of indicated preterm delivery in our study was 15%, which is similar to the rates of 16 and 22% reported in two previous studies (6,9). Progression of nephropathy, occurrence of preeclampsia, and HbA_{1c} >7% at delivery were all significantly associated with indicated preterm delivery. Among women with type 1 diabetes, the risk of preeclampsia and adverse neonatal outcomes is increased by the presence of a preexisting nephropathy (15,16). Furthermore, in women with type 1 diabetes and microalbuminuria, the prevalence of preterm delivery is considerably increased, mainly caused by preeclampsia (17). Although the presence of diabetic nephropathy, even in its early stages, identifies patients with increased risk of indicated preterm delivery, whether this may lead to prevention of preterm delivery is a matter of debate. In one study, preconceptional treatment with ACE inhibitors along with tight metabolic control in women with diabetic nephropathy has been reported to decrease the incidence of preeclampsia (17), but this was not reproduced in another study (18). The efficiency of low-dose aspirin for the prevention of preeclampsia in women with historical risk factors, including diabetes, has been recently reviewed (19). Based on this review, the efficiency of aspirin for the prevention of preeclampsia in women with type 1 diabetes appears to be mild. The association between nulliparity and preterm delivery is controversial. In our study, nulliparity was associated only with indicated preterm delivery. However, because indicated preterm delivery was mainly due to preeclampsia, which is also associated with nulliparity, we cannot exclude an interaction between these two risk factors.

Poor glycemic control was associated with both spontaneous and indicated preterm delivery. Our study did not allow the identification of the mechanisms of this association. However, it has been shown that hyperglycemia directly induces endothelial dysfunction and increased oxidative stress leading to blunted nitric oxide–dependent vasodilatation (20). During pregnancy, decreased synthesis of nitric oxide in the uterus is associated with initiation of labor in animals, and nitric oxide has been shown to be a uterine relaxant (21). To our knowledge, the effect of hyperglycemia on nitric oxide synthesis and/or activity in the myometrium has not been studied. These observations suggest that strict glycemic control might reduce the rate of preterm delivery and deserve further research.

In conclusion, the current study showed that the rate of preterm delivery remains high in women with type 1 diabetes. As in the general population, the causes of preterm delivery are not completely identified. In our study, different factors were associated with spontaneous and indicated preterm delivery. Because

poor glycemic control was a risk factor for both outcomes, part of preterm delivery might be preventable.

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