French Multicentric Survey of Outcome of Pregnancy in Women With Pregestational Diabetes

DIABETES AND PREGNANCY GROUP, FRANCE

OBJECTIVE — To evaluate perinatal outcome in pregnancies in women with type 1 and type 2 diabetes and the influence of preconception care 10 years after the St. Vincent's declaration.

RESEARCH DESIGN AND METHODS — A cross-sectional study was conducted in 12 perinatal centers in France in 2000–2001. The main investigated outcomes were perinatal mortality, major congenital malformations, and preterm delivery.

RESULTS — Among 435 single pregnancies, 289 (66.4%) were from women with type 1 and 146 (33.6%) from women with type 2 diabetes. Perinatal mortality rate was 4.4% (0.7% national rate), severe congenital malformations rate was 4.1% (2.2% national rate), and preterm delivery rate was 38.2% (4.7% national rate). Preconception care was provided in 48.5% women with type 1 diabetes and in 24.0% women with type 2 diabetes. Women whose first trimester HbA_{1c} was >8% had higher rates of perinatal mortality (9.2 vs. 2.5%; odds ratio 3.9; 95% CI 1.5–9.7; $P < 0.005$), major congenital malformations (8.3 vs. 2.5%; 3.5; 1.3–8.9; $P < 0.01$), and preterm delivery (57.6 vs. 24.8%; 1.4; 1.1–1.7; $P < 0.005$) than those with first trimester HbA_{1c} <8%. These results are similar to those reported in France in 1986–1988.

CONCLUSIONS — Pregnancies in women with diabetes are still poorly planned and complicated by higher rates of perinatal mortality and major congenital malformations. Despite knowledge of the importance of intensified glycemic control before pregnancy, reaching the St. Vincent's target needs further implementation in France.

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In 1989, representatives of the government health departments and patients' organizations from all of the European countries met with diabetes experts under the aegis of the Regional Offices of the World Health Organization and the International Diabetes Federation in St. Vincent, Italy, and identified goals to be achieved in the treatment of diabetes (1). One of the declared aims was that within 5 years, "pregnancy outcome of diabetic women should approximate that of the nondiabetic women." Previous studies have shown that such results may be obtained in women with type 1 diabetes by providing effective preconception care and intensive support to improve glycemic control before and during the whole pregnancy (2–5). However, this was achieved in selected populations and in specialized units. By contrast, several surveys done in nonselected, geographically based populations showed that the prognosis of pregnancy in women with type 1 diabetes remains poorer than that of the general population (6,7). Moreover, new issues have been raised by the increasing prevalence of type 2 diabetes in pregnancy (8). Particularly, type 2 diabetes often remains unrecognized, and the rate of perinatal mortality in women with type 2 diabetes may be higher than in those with type 1 diabetes (9).

In 1986–1988, a multicenter survey of pregnancies in women with diabetes was performed in France (10). It essentially showed that the rate of perinatal mortality was 1.9% in women with type 1 diabetes and that the rate of major congenital malformations was 4% in both women with type 1 and type 2 diabetes, both of which were above corresponding rates in the general population. The main objective of the present study was to assess whether outcomes of pregnancies in women with diabetes improved 10 years after the St. Vincent's targets have been defined.

RESEARCH DESIGN AND METHODS

— In 1998, a national Diabetes and Pregnancy Study Group was set up with the support of the French Association for the Study of Diabetes. Twelve tertiary perinatal centers, all members of this group, participated in the present study (see list in acknowledgments). All women with type 1 or type 2 diabetes and a single pregnancy who delivered between January 2000 and December 2001 were recruited for the study. Gestational diabetes and multiple pregnancies were excluded.

All data were prospectively collected using the Obstetrical Quality Indicators and Data Collection aggregated database (11), which consists of the following categorical variables: preconception care; HbA_{1c} >8% during the first and third trimesters; retinopathy, nephropathy, and their progression; gestational hypertension or pre-eclampsia; pregnancy outcomes (perinatal mortality, major congenital malformations, preterm delivery); macrosomia; mode of delivery; and neonatal complications.

Preconception care included information about the need for optimization of glycemic control before pregnancy, assessment of diabetes complications, review of dietary habits, intensification of capillary blood glucose self-monitoring (before and 2 h after each of the three

Address correspondence and reprint requests to Jacques Lepercq, MD, Service de Gynécologie-Obstétrique, Hôpital Cochin-Saint Vincent de Paul, 82, Avenue Denfert-Rochereau, 75674 Paris cedex 14, France. E-mail: j.lepercq@svp.ap-hop-paris.fr.

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

Table 1—*Maternal data in 435 pregnancies in women with type 1 and type 2 diabetes*

Parameters	Type 1 diabetes	Type 2 diabetes
n	289	146
Retinopathy	99 (34.3)	4 (2.7)
Nephropathy	34 (11.8)	7 (4.8)
First trimester HbA_{1c} >8%	88 (30.4)	32 (21.9)

Data are *n* (%).

main meals and at bedtime), and optimization of insulin therapy using three to five daily insulin injections or continuous subcutaneous infusion by 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. Delivery of preconception care was recorded by diabetologists. HbA_{1c} measured by high-performance liquid chromatography (normal 4.9 ± 0.6%) was obtained during the first trimester. Actual values of HbA_{1c} were not available because the Obstetrical Quality Indicators and Data Collection database only recorded HbA_{1c} >8%. Accordingly, a value <8% was considered as a surrogate marker of effective prepregnancy control. Retinopathy was classified as absent, mild nonproliferative, moderate nonproliferative, severe nonproliferative, or proliferative. Ophthalmologic examination was performed each trimester in women without retinopathy and monthly in those with retinopathy. Retinopathy progression was defined as a higher stage at last evaluation than that at baseline. Nephropathy was classified on the basis of prepregnancy urinary albumin excretion rate as absent (urinary albumin excretion rate <30 mg/24 h), incipient (30–300 mg/24 h), overt (>300 mg/24 h), or renal insufficiency (creatinine clearance <90 ml/min). Progression was defined as a higher stage at last evaluation than that at baseline. Gestational hypertension was defined, according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (12), as a systolic blood pressure level ≥140 mmHg or a diastolic blood pressure level ≥90 mmHg after 20 weeks of gestation on two occasions at least 6 h apart in women with previously normal blood pressure. Pre-eclampsia was defined by gestational hypertension associated with proteinuria ≥300 mg/24 h.

Fetal deaths were defined as stillbirths ≥22 weeks of gestation or an infant weighing ≥500 g. Neonatal death was defined as the death of a live born infant before the 28th day of life. Perinatal mortality comprised both fetal and neonatal deaths. Major congenital malformations were classified according to EUROCAT (13). Preterm delivery comprised delivery <37 weeks of gestation. Macrosomia was defined as a birth weight >4,000 g. Mode of delivery and neonatal complications (admission to the neonatal intensive care unit, respiratory distress syndrome) were collected.

Comparisons among groups were performed with the χ^2 test and Fisher's exact test when appropriate. Odds ratios (ORs) are reported with 95% CI. A logistic regression model was used to assess the role of independent variables on pregnancy outcomes. Statistical analysis was performed with StatView 5.0 software (SAS Institute, Cary, NC).

RESULTS — Complete information was available for 435 single pregnancies (289 type 1 diabetes, 146 type 2 diabetes). Maternal data at inclusion are reported in Table 1. During pregnancy, progression of retinopathy was reported in 39 women (39.4%) and progression of nephropathy in 23 women (67.6%). In addition, onset of retinopathy was reported in seven women and onset of nephropathy in five. Gestational hypertension or pre-eclampsia occurred in 54 (18.7%) patients with type 1 diabetes and in 26 (17.8%) patients with type 2 diabetes. Among the 41 women who had a pre-existing nephropathy, 21 developed gestational hypertension or pre-eclampsia, whereas this complication occurred in 20 of the 345 women without nephropathy (51.2 vs. 5.8%; OR 3.3; 95% CI 2.2–4.8; $P < 0.0001$). No association was found between a pre-existing retinopathy and the occurrence of gestational hypertension or pre-eclampsia.

The overall perinatal mortality rate was 4.4% (Table 2). Among the 19 perinatal deaths, 15 were stillbirths, 4 were neonatal deaths, and 8 were associated with major congenital malformations. Congenital malformations occurred in 18 infants (4.1%) born to type 1 diabetic mothers in 13 cases and to type 2 diabetic mothers in 5 cases (Table 2). Four terminations of pregnancy were performed because of major congenital malformations and two because of serious maternal complications (one severe renal insufficiency and one eclampsia).

The overall preterm delivery rate was 38.2%. Twenty-one pregnancies ended before 32 weeks of gestation (4.8%) and 145 (33.4%) between 32–37 weeks of gestation (106 relating to type 1 diabetes and 39 relating to type 2 diabetes). Among 420 live born infants, 126 (30.3%) were admitted to neonatal intensive care unit, and 44 (10.6%) had respiratory distress syndrome.

Among the 166 infants delivered before 37 weeks of gestation, preterm delivery was associated with maternal complications in 101 cases. In the univariate analysis, preterm delivery was associated with first trimester HbA_{1c} >8%, pre-existing retinopathy, pre-existing nephropathy, progression of a retinopathy, and gestational hypertension or pre-eclampsia. In the multivariate analysis,

Table 2—*Perinatal mortality and major congenital malformations in 435 pregnancies in women with type 1 and type 2 diabetes*

Parameters	Type 1 diabetes	Type 2 diabetes
n	289	146
Perinatal mortality	19 (6.6)	6 (4.1)
Stillbirth 22–27 weeks of gestation	8 (2.8)	2 (1.4)
Stillbirth >27 weeks of gestation	4 (1.4)	1 (0.7)
Neonatal mortality	1 (0.3)	3 (2.1)
Congenital malformations	13 (4.5)	5 (3.4)

Data are *n* (%).

Table 3—*Associated factors with preterm delivery*

	Univariate analysis	Multivariate analysis	
Parameters	*P*	*P*	OR (95% CI)
First trimester HbA_{1c} >8%	0.0004	0.002	2.2 (1.4–3.7)
Pre-existing retinopathy	0.03	0.5	1.2 (0.7–2.2)
Pre-existing nephropathy	0.0001	0.005	3.5 (1.5–8.6)
Deterioration of retinopathy	0.03	0.7	0.9 (0.4–1.9)
Gestational hypertension/pre-eclampsia	<0.0001	<0.0001	6.1 (3.4–11.0)

first trimester HbA_{1c} >8% (OR 2.2; 95% CI 1.4–3.7; $P = 0.002$), pre-existing nephropathy (3.5; 1.5–8.6; $P = 0.005$), and the occurrence of gestational hypertension or pre-eclampsia (6.1; 3.4–11.0; $P < 0.0001$) remained associated with preterm delivery (Table 3).

In 72 live born infants, birth weight was higher than 4,000 g (17.3%). A cesarean section was performed in 256 cases (58.9%), spontaneous vaginal delivery occurred in 145 cases (33.3%), and instrumental extraction was performed in 34 cases (7.8%). Among vaginal deliveries, 11 (7.6%) shoulder dystocia were reported, 7 infants weighed >4,000 g, and 4 infants weighed <4,000 g.

First trimester HbA_{1c} was >8% in 120 women (27.6%). Women whose HbA_{1c} was >8% had higher rates of perinatal mortality (9.2 vs. 2.5%; OR 3.9; 95% CI 1.5–9.7; $P < 0.005$), major congenital malformations (8.3 vs. 2.5%; 3.5; 1.3–8.9; $P < 0.01$), and preterm delivery (57.6 vs. 24.8%; 1.4; 1.1–1.7; $P < 0.005$) than those whose first trimester HbA_{1c} was <8%. First trimester HbA_{1c} was more frequently >8% in women who did not receive preconception care than in those who did (43.5 vs. 4.0%; 18.5; 8.3–40.9; $P < 0.001$). Influence of preconception care on prepregnancy control (i.e., first trimester HbA_{1c} >8%) and pregnancy outcome in women with type 1 diabetes and type 2 diabetes is reported in Tables 4 and 5.

CONCLUSIONS — Our data show that the outcome of pregnancy in women with type 1 and type 2 diabetes remains poor in France in 2000–2001.

Compared with French data obtained in the general population (14,15), a sixfold increase in perinatal mortality (national rate 0.7%), a twofold increase in major congenital malformations (national rate 2.2%), and an eightfold increase in preterm delivery (national rate for single pregnancy 4.7%) were observed. These results are similar to those reported in Northeast England in contrast to Norway (16), but selection biases have been suggested to explain these discrepancies (17). In the same respect, our study may have overestimated the risk of perinatal complications because participating centers are tertiary perinatal units recruiting high-risk pregnancies. The present results are identical to that obtained in a comparable study performed in 1986–1988 in France (10) and indicate that the targets of the St. Vincent's declaration have not been reached.

Our results confirm the dramatic deleterious effect of the absence of preconception care in women with type 1 diabetes because 80–90% of perinatal deaths and congenital malformations occurred in unplanned pregnancies and in women whose first trimester HbA_{1c} was >8%. We also observed a very high rate of preterm delivery similar to that recently reported (18). Both spontaneous and indicated preterm deliveries are increased in pregestational diabetes (18). First trimester HbA_{1c} >8%, a pre-existing nephropathty, and gestational hypertension or pre-eclampsia were independently associated with preterm delivery in our study.

The prevalence of type 2 diabetes was rather low (33.6%) in our study at variance with that reported elsewhere (8). This may be due to a lower prevalence of this disease in France, to an unrecognized condition, and/or to recruitment bias in tertiary perinatal centers. Type 2 diabetes was associated with a 4.1% perinatal mortality rate and a 3.4% congenital malformations rate in our study. These results are in accordance with others reporting a high perinatal mortality rate associated with type 2 diabetes (9). Only 24% of women with type 2 diabetes received preconception care in our study, and a poorer attendance for effective preconception care, later booking for antenatal care, and poorer glycemic control during pregnancy may all contribute to the high rate of congenital malformations and perinatal mortality (9,19).

Our results show that when preconception care was provided, prepregnancy glycemic control was better achieved, and the rate of perinatal complications was similar to that of the nondiabetic French population. However, even among women with type 1 diabetes who are followed at least biannually in diabetes centers, preconception care was not implemented in >50%. This rate is similar to the estimated frequency of unplanned pregnancies in the 1986–1988 French study (10) and in other surveys (20).

The way to enhance preconceptional enrollment remains unclear. Several factors may promote preconception care, including higher educational level, higher incomes, regular employment, and encouragement from health care providers to avoid unplanned pregnancies (21). Diabetes care providers should be warned of the failure of preconception care in women with diabetes. Furthermore, there is a need to improve access for all women with diabetes who are fertile to preconception care programs, including appropriate contraception. In this respect, patients' associations might be helpful.

Table 4—*Association among preconception care, prepregnancy control, and pregnancy outcome in 289 women with type 1 diabetes*

	Preconception care		
Parameters	Yes	No	*P*
Total	140 (48.5)	149 (51.5)	
First trimester HbA_{1c} >8%	6 (4.3)	82 (55.0)	<0.0001
Perinatal mortality	1 (0.7)	12 (8.1)	<0.005
Congenital malformation	1 (0.7)	12 (8.1)	<0.005

Data are *n* (%).

Table 5—*Association among preconception care, prepregnancy control, and pregnancy outcome in 146 women with type 2 diabetes*

Parameters	Preconception care		*P*
	Yes	No	
Total	35 (24.0)	111 (76.0)	
First trimester HbA_{1c} >8%	1 (2.9)	31 (27.9)	<0.001
Perinatal mortality	2 (5.7)	4 (3.6)	NS
Congenital malformation	1 (2.9)	4 (3.6)	NS

Data are *n* (%). NS, not significant.

Announcements in the media may also be efficient because, in one study, they led to enhanced preconceptional recruitment of type 1 diabetic women and to a reduction in perinatal mortality and malformation rates to general population levels (5).

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References

1. Workshop Report: Diabetes care and research in Europe: the Saint Vincent declaration. *Diabet Med* 7:360, 1990
2. Willhoite MB, Bennert HW, Palomaki GE, Zaremba MM, Herman WH, Williams JR, Spear NH: The impact of preconception counseling on pregnancy outcomes: the experience of the Maine Diabetes in Pregnancy Program. *Diabetes Care* 16:450–455, 1993
3. Kitzmiller JL, Buchanan TA, Kjos S, Combs CA, Ratner RE: Pre-conception care of diabetes, congenital malformations, and spontaneous abortions. *Diabetes Care* 19:514–541, 1996
4. The Diabetes Control and Complication Trial Research Group: Pregnancy outcomes in the diabetes control and complications trial. *Am J Obstet Gynecol* 174: 1343–1353, 1996
5. McElvy SS, Miodovnik M, Rosenn B, Khoury JC, Siddiqi T, Dignan PS, Tsang RC: A focused preconceptional and early pregnancy program in women with type 1 diabetes reduces perinatal mortality and malformation rates to general population levels. *J Matern Fetal Med* 9:14–20, 2000
6. Casson IF, Clarke CA, Howard CV, McKendrick O, Pennycook S, Pharoah PO, Platt MJ, Stanisstreet M, van Velszen D, Walkinshaw S: Outcomes of pregnancy in insulin dependent diabetic women: results of a 5-year population cohort study. *BMJ* 315:275–278, 1997
7. Hawthorne G, Robson S, Ryall EA, Sen D, Roberts SH, Ward Platt MP: Prospective population based survey of outcome of pregnancy in diabetic women: results of the Northern Diabetic Pregnancy Audit, 1994. *BMJ* 315:279–281, 1997
8. Engelgau MM, Herman WH, Smith PJ, German RR, Aubert RE: The epidemiology of diabetes and pregnancy in the U.S., 1988. *Diabetes Care* 18:1029–1033, 1995
9. Cundy T, Gamble G, Townsend K, Henley PG, MacPherson P, Roberts AB: Perinatal mortality in type 2 diabetes mellitus. *Diabet Med* 17:33–39, 2000
10. Gestation and Diabetes in France Study Group: Multicenter survey of diabetic pregnancy in France. *Diabetes Care* 14:994–1000, 1991
11. Johansen KS, Hod M: Quality development in perinatal care: the OBSQID project. Obstetrical Quality Indicators and Data. *Int J Gynaecol Obstet* 64:167–172, 1999
12. Report of the National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy. *Am J Obstet Gynecol* 183 (Suppl. 1):S1–S22, 2000
13. Lechat MF, Dolk H: Registries of congenital anomalies: EUROCAT. *Environ Health Perspect* 101 (Suppl. 2):153–157, 1993
14. Blondel B, Norton J, du Mazaubrun C, Breart G: Development of the main indicators of perinatal health in metropolitan France between 1995 and 1998: results of the national perinatal survey. *J Gynecol Obstet Biol Reprod (Paris)* 30:552–564, 2001
15. Stoll C, Ayme S, Beckers R, Calzolari E, Cornel M, Cushieri A, De Wals P, Dolk H, Dott B, Galanti C: Distribution of single organ malformations in European populations: EUROCAT Working Group. *Ann Genet* 38:32–43, 1995
16. Hawthorne G, Irgens LM, Lie RT: Outcome of pregnancy in diabetic women in northeast England and in Norway, 1994–1997. *BMJ* 321:730–731, 2000
17. Golding J: Outcome of pregnancy in diabetic women: more investigation is needed into whether control of diabetes is really poorer in England than Norway. *BMJ* 322:614–615, 2001
18. Sibai BM, Caritis SN, Hauth JC, MacPherson C, VanDorsten JP, Klebanoff M, Landon M, Paul RH, Meis PJ, Miodovnik M, Dombrowski MP, Thurnau GR, Moawad AH, Roberts J: Preterm delivery in women with pregestational diabetes mellitus or chronic hypertension relative to women with uncomplicated pregnancies: the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol* 183:1520–1524, 2000
19. Brydon P, Smith T, Proffitt M, Gee H, Holder R, Dunne F: Pregnancy outcome in women with type 2 diabetes mellitus needs to be addressed. *Int J Clin Pract* 54: 418–419, 2000
20. American Diabetes Association: Preconception care of women with diabetes. *Diabetes Care* 26 (Suppl. 1):S91–S93, 2003
21. Janz NK, Herman WH, Becker MP, Charron-Prochownik D, Shayna VL, Lesnick TG, Jacober SJ, Fachnie JD, Kruger DF, Sanfield JA, et al: Diabetes and pregnancy: factors associated with seeking pre-conception care. *Diabetes Care* 18:157–165, 1995