Multicenter Survey of Diabetic Pregnancy in France

Gestation and Diabetes in France Study Group

Objective: To describe the medical care and outcome of diabetic pregnancy and gestational diabetes in France and study their associations with glycemic control. Research Design and Methods: We performed a multicenter prospective survey with systematic collection of clinical and biological data (HbA_{1c} analysis in a central laboratory) at five successive examinations and consecutive recruitment of women at any stage of pregnancy in 46 specialized centers from all parts of France. Pregnancies were followed to the end. There were 483 single pregnancies (232 women with insulin-dependent diabetes mellitus [IDDM], 78 with non-insulin-dependent diabetes mellitus [NIDDM], and 173 with gestational diabetes mellitus [GDM]), and 11 twin births (8 IDDM, 3 GDM). Results: We observed 30 abortions (6%), 8 perinatal deaths (1.8%, 4 IDDM, 4 GDM), and 13 congenital malformations (3%). In the 11 twin pregnancies, there were 7 congenital malformations. Premature births and cesarean sections were found very frequently (42 and 61% IDDM, 29 and 55% NIDDM, 22 and 32% GDM, respectively). In the three groups, birth weight adjusted for gestational age was much greater than national reference values. HbA_{1c} levels during the first trimester were significantly higher in women who aborted (mean ± SE 7.1 ± 0.4 vs. 5.6 ± 0.1%, $P < 0.001$) and those who gave birth to malformed infants (6.8 ± 0.4 vs. 5.9 ± 0.1%, $P < 0.05$). Conclusions: Perinatal mortality was slightly higher in diabetic women than the general population (1.8 vs. 1.2%), but the prematurity rate was much higher, possibly due to an interventionist policy in some centers. Fetal loss and congenital malformations were associated with poor glycemic control. *Diabetes Care* **14:994–1000, 1991**

Over the last 40 yr, perinatal mortality has decreased considerably in pregnancies complicated by diabetes mellitus (1–3). However in most industrialized countries, the rate of congenital abnormalities remains two or three times higher in diabetic pregnancies than other pregnancies (1,3,4). These studies, which were set up to verify hypotheses and identify risk factors, do not reflect the nationwide level of care. The epidemiological evaluation of the risk encountered by fetuses of diabetic mothers has been described rarely in unselected populations, because this presupposes either a systematic referral to some highly specialized centers or a large multicenter framework. The British survey of diabetic pregnancies (5) concluded that the most common complication in permanent diabetes was premature delivery (50% established diabetes, 22% gestational diabetes mellitus [GDM]) associated with a high rate of congenital malformations (5.7% established diabetic cases, 1.8% GDM). In the United States, a study of all births in Washington state (either live births or fetal deaths ≥20 wk gestation) during 1979 and 1980 showed that the risk of perinatal mortality among infants of women with pre-existing diabetes mellitus was about eight times the state perinatal mortality rate (6). In another study conducted in five centers between 1980 and 1985, diabetic women who enrolled within 21 days of conception were compared with a control group and diabetic women who entered the study later (7). The malformation rate was higher among

From the National Institute of Health and Medical Research (INSERM), Paris, France.

Address correspondence and reprint requests to Muriel Vray, Institut National de la Santé et de la Recherche Médicale U.21, 16 Avenue Paul Vaillant-Couturier, F94807 Villejuif Cedex, France.

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offspring of diabetic women followed early in their pregnancy (4.9%) than among the control group (2.1%) and much higher among those followed later (9%).

In France, diabetes control and care and outcome of diabetic pregnancies have never been studied nationally; there is no systematic referral to specialized centers where such data could be collected. Therefore, in 1986, we decided to undertake a prospective multicenter survey involving numerous diabetes centers from all parts of the country. The aims of this study were to *1*) assess the usual practical medical care and outcome of pregnancies among diabetic women in France, *2*) describe those women screened as GDM, and *3*) study the relationships between glycemic control and pregnancy outcome.

RESEARCH DESIGN AND METHODS

Pregnant women were recruited from 46 diabetes centers between May 1986 and October 1988. Patients were eligible if they were pregnant, had been seen for the first time in the diabetes center for the current pregnancy, and either known to have diabetes before their pregnancy (insulin-dependent diabetes mellitus [IDDM], treated with insulin; non-insulin-dependent diabetes mellitus [NIDDM], treated with oral drugs and/or diet) or detected as GDM. A 75-g oral glucose tolerance test (OGTT), as recommended by the World Health Organization (8), was performed to diagnose pregnant women not known previously to have diabetes with the following criteria: fasting plasma glucose >5.5 mM and/or 2 plasma glucose >7.8 mM. Patients were excluded if they had renal failure or chronic hemolysis that could interfere with the HbA_{1c} level.

Five clinical examinations were planned during pregnancy: ≤8, 9–16, 17–24, 25–32, and ≥33 wk. Inclusion in the survey was possible at any stage of gestation. At inclusion, baseline characteristics, information concerning diabetes (date of diagnosis, treatment before pregnancy, diabetic complications such as retinopathy, and proteinuria, and obstetrical history (number of previous pregnancies, spontaneous or therapeutic abortions, cesarean sections, stillbirths, malformations) were collected. Weight, blood pressure, acute complications of diabetes, fasting and postprandial blood glucose (analyzed locally [glucose oxidase]), and HbA_{1c} analyzed in a central laboratory by high-performance liquid chromatography, were measured at each examination. At the end of pregnancy, data concerning gestational age (confirmed by ultrasound, temperature curve, and/or menstrual cycle), mode of delivery, and the newborn (weight, sex, blood glucose level measured by glucose oxidase, hypocalcemia, jaundice, polycythemia, respiratory distress, cardiac failure, congenital malformations) were collected.

Neonatal complications were defined as *1*) hypocalcemia (at least 1 plasma Ca^+ level <1.7 mM before 5th day of life); *2*) polycythemia sampled in the peripheral venous blood with either hematocrit >70% or hemoglobin >230 g/L); *3*) jaundice (clinical criteria and/or bilirubinemia >260 μM); *4*) respiratory distress (transient, no ventilation, or ventilation for <48 h or prolonged ventilation for >48 h); *5*) cardiac failure (cardiomegaly [cardiothoracic index >0.5] plus tachycardia plus hepatomegaly); and 6) congenital malformations, assessed for each case by a panel of pediatricians. Complications of the pregnant mother were defined as *1*) pregnancy-induced hypertension (PIH; diastolic blood pressure >90 mmHg on 2 or more occasions in a previously normotensive woman); *2*) preeclampsia (PIH with 2+ proteinuria); *3*) urinary infection (bacteriuria [$\geq 10^5$ bacteria/ml] either asymptomatic or associated with febrile pyelonephritis); *4*) proteinuria (>0.5 g/L), and *5*) diabetic retinopathy (presence of microaneurysms and/or spot hemorrhages [background], neovessels, or vitreous hemorrhages [proliferative]).

Infant birth weight was adjusted according to the gestational age at delivery. For each observed birth weight, the difference from the national mean birth weight (9) at that gestational age was calculated and then divided by the corresponding SD. Intrauterine growth retardation was defined if the adjusted birth weight was <10th percentile and macrosomia if >90th percentile of the distribution of this index. We also measured the body mass index (BMI; kg/m^2) of the mothers and the perinatal mortality rate (9) (no stillbirths + no neonatal deaths)/(no live births + no stillbirths).

Statistical analysis. Data management and analysis were performed with BMDP (10) on the VAX computer of the Institut National de la Santé et de la Recherche Médicale. χ^2 and Student's *t* tests and analysis of variance were used for comparisons. *P* refers to the analysis of variance of the three groups of patients. Results were expressed as means ± SE. Data presented in the tables and text refer to single pregnancies unless stated.

RESULTS

Complete information was available for 483 single pregnancies. Diabetes was known before pregnancy in 310 patients (232 IDDM, 78 NIDDM [25% of known diabetic cases]). Diabetes was diagnosed during pregnancy in 173 women, and 12 of them had only an abnormal fasting blood glucose value. Eleven additional patients who had a twin pregnancy are described separately for congenital malformations and perinatal mortality only.

IDDM patients were younger, leaner, more often primigravida, and had less chronic hypertension than NIDDM patients or women with GDM (Table 1). Multiparous IDDM women had the highest rates of previous cesarean section, stillbirth, and spontaneous abortion. Retinopathy was more frequent in IDDM than NIDDM women. Fifty-two percent of known diabetic women mentioned that they were not followed by a diabetologist before their pregnancy and that they then attended the diabetes center for the first time.

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TABLE 1
Baseline maternal characteristics in IDDM, NIDDM, and GDM in single pregnancies

	IDDM (*n* = 232)	NIDDM (*n* = 78)	GDM (*n* = 173)
Age (yr)*	27.3 ± 0.3	32.7 ± 0.7	31.3 ± 0.4
Smokers (% ≥1 cigarette/day)	28	21	24
BMI before pregnancy (kg/m^2)*	22.2 ± 0.2	27.2 ± 0.8	27.6 ± 0.5
Duration of diabetes (yr)*	11.0 ± 0.4	5.2 ± 0.5	
Arterial hypertension (%)†	9	19	15
Retinopathy			
Not proliferative (%)	23	2	0
Proliferative (%)	7	0	0
Proteinuria (%)	6	4	0
Primigravida (%)*	37	15	18
Previous perinatal death (%)	11	9	5
Previous cesarean section (%)*	50	15	11
Previous spontaneous abortion (%)‡	25	17	16

Values are means ± SE for quantitative variables.
IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; GDM, gestational diabetes mellitus.
*$P < 0.001$.
†Before or during 1st trimester of current pregnancy.
‡$P < 0.05$.

According to White's classification of diabetes in IDDM women, 25% of the women were in class B, 40% in class C, 25% in class D, and 10% in class R-F.

Maternal follow-up and complications. On average, IDDM patients went to the diabetes center earlier than the other women for their 1st visit after conception ($P < 0.001$; Table 2). Fifty percent of IDDM and 40% of NIDDM women entered the study before 8 wk of gestation, whereas only 24% of GDM women attended the diabetes center before 24 wk of gestation.

Most NIDDM (85%) and nearly half of the GDM (45%) women were insulin treated during their pregnancy. There were no oral antidiabetic drugs prescribed. Seventy percent of the patients were hospitalized one or more times before delivery.

The frequency of urinary infection (22% overall), pregnancy-induced hypertension (13% overall), and preeclampsia (3% overall) was found not to be significantly different among the three groups.

Pregnancy outcome. Four abortions were induced for medical reasons: one case of Down's syndrome in the fetus of a woman with GDM and three other cases in IDDM patients, one case of fulminating arterial hypertension plus proliferative retinopathy at 22 wk, one case of maternal toxoplasmosis, and one case of renal insufficiency (Table 3). No abortion was induced because of malformation. Spontaneous abortions occurred in 27 of 310 (9%) diabetic mothers. The 2% rate of abortions in the GDM group is probably widely underestimated, because most of these cases were recruited after the first trimester. Among the 249 mothers with available data, glucose control was significantly poorer during the first trimester of pregnancy in the 23 patients who aborted spontaneously (HbA_{1c} 7.1 ± 0.4 vs. 5.6 ± 0.1%, $P < 0.001$; and fasting blood glucose 9.5 ± 0.9 vs. 6.7 ± 0.2 mM, $P < 0.001$).

Fetal death occurred in four cases among IDDM patients, four in GDM patients, and none in NIDDM patients (Table 3). There were no early neonatal deaths (<8 days of life), but there were two late neonatal deaths (8–28 days of life). The first case was from an IDDM mother who delivered by cesarean section at 29 wk because of severe preeclampsia; the newborn weighed 1000 g, suffered from hyaline membrane disease, and died at day 13. The second neonate, from a woman with GDM who delivered at 37 wk, died at day 8 from meningitis (2500 g birth weight). Thus, for the whole sample, the perinatal mortality rate was 1.8% in single births.

Gestational age at delivery was lower in IDDM women than the other two groups ($P < 0.001$; Table 4) Accordingly, the prematurity rate (delivery before 37 complete wk of pregnancy) was higher in IDDM women ($P < 0.001$).

The high frequency of cesarean sections observed in the three groups has to be underlined, particularly in primigravida women (Table 4). As expected, delivery by cesarean section was found to be related to previous cesarean sections (47 vs. 12% in those without antecedent, $P < 0.001$) but also to the glycemic control at the end of pregnancy (5.00 ± 0.07% in women who delivered by cesarean section vs. 4.60 ± 0.06% in those delivering vaginally, $P < 0.001$) and to the presence of progressive retinopathy (15% in women who delivered

TABLE 2
Follow-up during pregnancy in IDDM, NIDDM, and GDM in single pregnancies

	IDDM (*n* = 232)	NIDDM (*n* = 78)	GDM (*n* = 173)
Gestational age at 1st visit to diabetes center (wk)*†	10.8 ± 0.4	14.4 ± 1.1	28.6 ± 0.6
Insulin treated (%)	100	85	45
Urinary infection (%)	25	24	17
PIH (%)	14	11	12
Preeclampsia (PIH + proteinuria; %)	4	2	1

Values are means ± SE for quantitative variables.
IDDM, insulin-dependent diabetes mellitus; NDDM, non-insulin-dependent diabetes mellitus; GDM, gestational diabetes mellitus; PIH, pregnancy-induced hypertension.
*Excluding abortions (induced or spontaneous).
†$P < 0.001$.

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TABLE 3
Outcome of single pregnancies in IDDM, NIDDM, and GDM

	IDDM (n = 232)	NIDDM (n = 78)	GDM (n = 173)	Total (n = 483)
Total fetal loss (%)	12 (29)	12 (9)	5 (9)	10 (47)
Spontaneous abortions <20 wk (%)	8 (19)	10 (8)	2 (3)	6 (30)
Induced abortions (n)				
Medical reasons (n)	3	0	1	4
Social reasons (n)	2	1	0	3
Stillbirths ≥28 wk (n)	4	0	4	8
Live births (n)	204	69	165	438
Late neonatal deaths 8–28 days (n)	1	0	1	2
Perinatal mortality rate (per 1000 births)	19.2 (4)		23.7 (4)	17.9 (8)
Malformations (%)	4 (9)	4 (3)	1 (1)	3 (13)

Number of cases in parentheses. There were no early (≤7 days after birth) neonatal deaths.
IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; GDM, gestational diabetes mellitus.

by cesarean section vs. 4% in those who did not, $P < 0.001$).

Despite the difference in gestational age, there was no significant difference in the average crude birth weight between the three groups (Table 4). The percentage of macrosomia was highest in NIDDM mothers (41%). In patients known previously with diabetes, mean adjusted birth weight was significantly lower in women with HbA_{1c} levels <6% after 33 wk gestation (0.62 ± 0.04 vs. 0.99 ± 0.16, $P = 0.05$).

Intrauterine growth retardation occurred in eight IDDM and eight GDM mothers and was highly related to hypertension (8.3% in hypertensive vs. 1.1% in normotensive mothers, $P < 0.001$).

Congenital malformations occurred in 13 fetuses including 12 from mothers previously diagnosed as diabetic (Table 3). When classified by system, malformations were distributed as genitourinary ($n = 2$), musculoskeletal (4), cardiac (3), pulmonary adenomatosis (1), and multisystem anomaly (3). Among the 214 women who had their first examination during the first trimester, HbA_{1c} levels at that time were significantly higher in the group who ultimately gave birth to malformed infants (6.8 ± 0.4 vs. 5.9 ± 0.1%, $P < 0.05$). A similar trend was observed with postprandial blood glucose values, although this was not significant ($P = 0.40$).

From the 11 twin births (8 IDDM mothers, 3 GDM mothers), 22 live-born infants were delivered. Seven cases of congenital malformations were observed, all of them in IDDM mothers, of which 5 led to late neonatal death (>7 days). When twin pregnancies were taken into account, the rate of congenital malformations in mothers previously known to have diabetes increased to 6.4%, but the rate of perinatal mortality was not changed.

Apart from congenital malformations, different pathological events were observed in single births (Table 5). Three infants of GDM mothers had Down's syndrome. Perinatal morbidity was highest among the infants of IDDM mothers and lowest in GDM mothers. The most common clinical features were jaundice (16%) and respiratory distress (15%) including 4.5% with prolonged ventilation. Infants with prolonged respiratory distress syndrome had a shorter gestational time (34.2 ± 0.7 vs. 37.8 ± 0.1 wk, $P < 0.001$), and HbA_{1c} level in the third trimester was higher (5.6 ± 0.34 vs. 4.8 ± 0.05%, $P < 0.001$). Cardiomegaly occurred in 10 children and cardiac failure in 4.

CONCLUSIONS

This study is the first prospective observational survey conducted nationally on pregnant diabetic women in France. The availability of reference data from national statistics allows for the comparison of the results observed in this sample of diabetic mothers to the general population. The standardized follow-up schedule included blood sampling to assess glycemic control with centralized determinations of HbA_{1c}, but routine medical practice was not changed during the survey.

In this series, the perinatal mortality rate was 1.8%; if postneonatal mortality is included, the rate was 2.4%. In IDDM mothers, perinatal mortality was 1.9%, which

TABLE 4
Duration of pregnancy, mode of delivery, and infant birth weight in women with IDDM, NIDDM, and GDM in single pregnancies

	IDDM (n = 204)	NIDDM (n = 69)	GDM (n = 165)
Gestational age at delivery (wk)*	36.9 ± 0.2	38.0 ± 0.2	38.3 ± 0.2
Premature delivery <37 wk (%)*	42 (86)	29 (20)	22 (36)
Cesarean section (%)			
Overall*	61 (125)	55 (38)	32 (52)
Primigravida (n = 119)†	62 (48)	45 (5)	32 (10)
Birth weight (g)	3355 ± 45	3519 ± 68	3353 ± 39
>90th percentile†	32 (65)	41 (28)	26 (42)
<10th percentile	4 (8)	0	5 (8)

Values are means ± SE for quantitative variables. Number of cases in parentheses for categorical variables. IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent mellitus; GDM, gestional diabetes mellitus.
*$P < 0.001$.
†$P < 0.05$.

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TABLE 5
Perinatal morbidity in single live-born infants of women with IDDM, NIDDM, and GDM

	IDDM (n = 204)	NIDDM (n = 69)	GDM (n = 165)
Glycemia (<3 mM; %)*	47 (96)	41 (28)	25 (41)
Hypocalcemia (<1.7 mM; %)†	11 (22)	4 (3)	3 (4)
Polycythemia (%)	6 (13)	3 (2)	2 (4)
Jaundice (%)	19 (39)	16 (11)	13 (21)
Respiratory distress (%)			
Transient†	16 (31)	13 (9)	7 (12)
Prolonged	7 (15)		3 (5)
Cardiomegaly (%)	3 (7)	0.01 (1)	0.01 (2)
Cardiac failure (%)	1 (3)		0.006 (1)

Number of cases in parentheses.
IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus; GDM, gestational diabetes mellitus.
*$P < 0.001$.
†$P < 0.01$.

is among the lowest published rates from specialized centers (1). Nevertheless, this rate is still higher than the national rate of 1.2% (9).

The rate for major congenital malformations in single births was 4% in both IDDM and NIDDM diabetic mothers, with none resulting in perinatal death. This rate is slightly lower than in the 1982 British survey (5.7%) and the other published series (1,5,11). The last national statistics gave a frequency of congenital malformations of 2.6% (9). Valid comparisons of these different rates are hindered by the lack of uniformity in the classification of congenital malformations.

Fuhrmann et al. (11) found in a study of 128 diabetic women that intensive treatment begun before conception was associated with only 0.8% malformations. In contrast, the incidence of major abnormalities was 7.5% in 292 diabetic women who sought care after 8 wk of gestation. Damm and Molstead-Pedersen (12) found that, among a group of carefully planned diabetic pregnancies, the major congenital malformation rate was only 1% compared to 1.7% in a control group. In our survey, glycemic control during gestation was related to the occurrence of congenital malformations. This result is consistent with the findings of Miller et al. (13) in the population attending the Joslin Clinic and the Boston Hospital for Women, Ylinen et al. (14) in 142 IDDM women followed at the central hospital of Helsinki, and more recently Lucas et al. (15). In contrast, in a large group of insulin treated women enrolled within 21 days of conception, Mills et al. (7) failed to show any difference in glycemic control between women whose infants were malformed and those with normal infants.

It seems that glycemic control also plays a role in spontaneous abortions; they appear to be associated with poor glycemic control during the first trimester in comparison with pregnancies going on to delivery. This finding is consistent with several studies and suggests the relevance of strict blood glucose control at the very beginning of gestation in diabetic women (16,17).

An important finding is the high frequency of preterm delivery and cesarean section compared with national rates, 5.6 and 10.6%, respectively (9). Similar rates were observed in the British survey (5). These figures are higher than the prematurity rate of 26% in insulin-requiring patients of the Joslin Clinic (18), which was less than three times the rate in the control population. In this study, the relative risk in pregnancies complicated by diabetes varied from 3.9 in GDM to 7.5 in IDDM women. This high rate could be partly explained by an interventionist delivery policy. It has been repeatedly stressed for >10 yr that diabetic mothers may and must deliver at term, i.e., after 37 complete wk of gestation. In the absence of obstetric indications, the spontaneous onset of labor should be awaited (19,20). It could be asked whether this message has been fully received by French obstetricians. However, the decision to perform a cesarean section seemed to rely not only on obstetric considerations but also in some cases on the diabetic status of the mother, as suggested by the relationship to glycemic control and the presence of progressive retinopathy.

Regarding intrauterine growth retardation, the rate was similar to that of the general population and was related significantly to the presence of hypertension.

As to the health status of the newborn, respiratory distress was the most frequent pathology (14.7%), including 4.5% who required assisted ventilation (national rate 1.8%). These were among the highest values of the published series, which showed rates ranging from 2.7 to 28.2% (1,21). The variability of the results from different studies probably partly reflects variations in prematurity and differences in the clinical definition of this complication. Apart from respiratory distress, neonatal morbidity (hypocalcemia, polycythemia, jaundice) occurred to the same extent as in the literature. The proportions of macrosomia are in agreement with most published series. Mean birth weight adjusted according to gestational age is slightly higher in women with HbA_{1c} values >6% after 33 wk of gestation. In other studies, birth weight was also found to be related to metabolic control during the last weeks of pregnancy (22,23).

Comparative analysis of our subgroups showed that the characteristics of NIDDM patients were very close to those of women with GDM and significantly different from those of IDDM patients in age, parity, BMI, and incidence of chronic arterial hypertension. In 41 of 173 (24%) cases of GDM, the first visit to a diabetologist occurred before 24 wk, so diabetes could be considered to have antedated pregnancy. This is consistent with the hypothesis of Harris (24), who wondered whether GDM is not in fact, in most cases, unrecognized NIDDM. This suggests that some of the 173 cases could have been detected earlier.

Overall, as in the literature, we found in this population, a slight excess of perinatal mortality and malformations. A higher risk is observed in twin pregnancies

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in IDDM patients with a malformation rate as high as 32%, leading to death in the 1st yr of life in most cases.

This study has shown that better glycemic control is associated with lower rates of spontaneous abortions and may contribute to lower rates of malformations. Therefore, it seems worthwhile to promote close collaboration between diabetologists and obstetricians at a regional level.

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APPENDIX 1: GDF STUDY GROUP

Scientific Committee: Jean-Jacques Altman, MD; Jean-Marcel Brun, MD; Philippe Chanson, MD; Patrick Fénichel, MD; Arnaud Murat, MD; Jean-Pierre Tauber, MD; Georges Tchobroutsky, MD; Francis Thervet, MD (Diabetology); Catherine Tchobroutsky, MD (Obstetrics); Bernard Salle, MD (Pediatrics); Jean Rosa, MD (Biology); Eveline Eschwege, MD; Laure Papoz, PhD; Dominique Simon, PhD (Epidemiology).

Diabetology: Jean-Jacques Altman, MD (Paris); Arnaud Murat, MD (Nantes); Simone Moinade, MD (Clermont-Ferrand); Guy Sery, MD (Nancy); Patrick Hassler, MD (Haguenau); Marie-Agnès Roques, MD (Angers); Jean-Marcel Brun, MD (Dijon); Philippe Chanson, MD (Paris); Didier Charitanski, MD (Dreux); Thierry Constans, MD (Tours); Régine Rouaud, MD (Montpellier); Erick Verlet, MD (Dunkerque); Robert Boizel, MD (Grenoble); Marie-Florence Verger, MD (Pontoise); Henri Gin, MD (Bordeaux); André Grimaldi, MD (Paris); Daniel Ben Soussan, MD (Valenciennes); Michel Malinsky, MD (Thionville); Richard Maréchaud, MD (Poitiers); Christine Chateauneuf, MD (Toulouse); Pierre François, MD (Clamart); Geneviève Ozenne, MD (Boisguillaume); Sylvie Wahl, MD (Vichy); Sylvie Arlot, MD (Amiens); Jean-Pierre Cappoen, MD (Lille); Annie Gross, MD (Reims); Jean-Pierre Le Floch, MD (Créteil); Isabelle Navez, MD (Toulouse); Dominique Simon, MD (Créteil); Jacqueline Dugay, MD (Le Mans); Jean-Pierre May, MD (Lille); Patrick Fénichel, MD (Nice); Véronique Llorca, MD (Besançon); Brigitte Rebattu, MD (Lyon); Pierre Thomas, MD (Roubaix); Pierre Valensi, MD (Paris); Bernard Canivet, MD (Nice); Pierre Chopinet, MD (Annecy); Françoise Duron, MD (Paris); Bernard Hubschman, MD (Arras); Claude Le Devehat, MD (Pougues-les-eaux); Luc Marty, MD (Carcassonne); Didier Halimi, MD (Créteil); Dominique Houlbert, MD (Alençon); Jacques Kressmann, MD (Lyon); Dominique Paris-Bockel, MD (Strasbourg).

HbA_{1c} Determination (INSERM U91, Créteil): Claude Prehu, MD; Yves Blouquit, PhD; Jean Rosa, PhD.

Coordination and Data Analysis (INSERM U21, Villejuif): Muriel Vray, MSc; Edith Garat, Bac; Laure Papoz, PhD (Principal coordinator).

Report Preparation: Catherine Tchobroutsky, MD (Maternité de Port-Royal, Paris); Muriel Vray MSc; Laure Papoz, PhD (INSERM U21, Villejuif).

Lilly France: Nicole Larpent, MD.

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