Outcomes in Type 1 Diabetic Pregnancies

A nationwide, population-based study

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OBJECTIVE — The aim of this study was to compare pregnancy outcomes in type 1 diabetic pregnancies with the background population.

RESEARCH DESIGN AND METHODS — This nationwide prospective multicenter study took place in eight Danish centers treating pregnant women with type 1 diabetes during 1993–1999. A total of 990 women with 1,218 pregnancies and delivery after 24 weeks (n = 1,215) or early termination due to severe congenital malformations (n = 3) were included. Data were collected prospectively by one to three caregivers in each center and reported to a central registry.

RESULTS — The perinatal mortality rate was 3.1% in type 1 diabetic pregnancies compared with 0.75% in the background population (RR 4.1 [95% CI 2.9–5.6]), and the stillbirth rate was 2.1% compared with 0.45 (4.7 [3.2–7.0]). The congenital malformation rate was 5.0% in the study population and 2.8% (1.7 [1.3–2.2]) in the background population. Six of the perinatal deaths (16%) were related to congenital malformations. Only 34% of women performed daily home monitoring of blood glucose at conception, and 58% received preconceptional guidance. Pregnancies with serious adverse outcomes (perinatal death and/or congenital malformations) were characterized by higher HbA_{1c} values before and during pregnancy and a lesser degree of maternal self-care and preconceptional guidance. Women who performed daily self-monitoring of blood glucose at any time during pregnancy had lower HbA_{1c} values than women who did not measure their daily profile. Likewise, daily self-monitoring was associated with a reduction in serious adverse outcomes. The caesarean section rate was 55.9 and 12.6%, respectively, and the risk of preterm delivery was 41.7 and 6.0%, respectively.

CONCLUSIONS — Type 1 diabetic pregnancies are still complicated by considerably higher rates of severe perinatal complications compared with the background population, and women with poor self-care are at the highest risk. Adequate glycemic control using daily glucose monitoring before and during pregnancy is a crucial step toward reaching the goals of the St. Vincent declaration.

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

In 1989, the St. Vincent declaration (1) stated that the outcome of diabetic pregnancy should approximate that of the nondiabetic pregnancy within 5 years. Since then, four regional prospective studies from the U.K. and Finland (2–5) and two nationwide studies from Holland and France (6,7) have reported rates for perinatal mortality and/or congenital malformations, considerably higher than the background population. The number of pregnancies varied from 111 to 691. In Denmark, clinical data have been prospectively collected since 1992, which enables us to analyze data on a cohort of >1,200 consecutive pregnancies. The objective was to compare pregnancy outcomes in type 1 diabetic pregnancies with the background population.

RESEARCH DESIGN AND METHODS

— During 1993–1999, all pregnancies in women with pregestational type 1 diabetes were prospectively reported to a central registry in the Danish Diabetes Association. The patients delivered in eight centers: four university hospitals (Copenhagen, Aarhus, Aalborg, and Odense) and four county hospitals (Esbjerg, Fredericia, Herning, and Hillerød) with special interest in diabetes and pregnancy. Information of maternal demography, diabetes status, and pregnancy outcome were collected after each delivery by one to three caregivers per center. All patients gave informed consent, and the local ethic committees approved the study. Inclusion criteria were delivery after 24 completed weeks (n = 1,215) or termination before 24 weeks because of ultrasound-verified severe malformation (n = 3). Abortions before 24 weeks for other reasons were not registered.

Local assays for HbA_{1c} were used. Correction was made to a common standard (normal range of standard assay, 0.044–0.064) by multiplying the HbA_{1c} value with a correction factor (mean of the reference values for a standard assay divided by the mean of the reference values for the given assay). The assays for HbA_{1c} were subjected to thorough quality control during this period. The coverage of

Table 1—*Obstetric complications and fetal characteristics for type 1 diabetic pregnancies and the background population*

	Type 1 diabetic pregnancy	Background population	RR (95% CI) or *P*
n	1,215	70,089	
Pre-eclampsia*	220 (18.1%)	*	<0.001
Caesarean section	680 (55.9%)	8,831 (12.6%)	4.4 (4.1–4.8)
Preterm delivery†	507 (41.7%)	4,205 (6.0%)	7.0 (6.3–7.6)
Gestational age at delivery (days)	256 ± 16	280	<0.0001
Birth weight (g)	3,487 ± 817	3,478	0.71
Birth weight ≥4,500 g	97 (8.0%)	2,383 (3.4%)	2.3 (1.9–2.9)
Large for gestational age infant‡	761 (62.5%)	—	<0.001
Stillbirth	26 (2.1%)	318 (0.45%)	4.7 (3.2–7.0)
Perinatal mortality	38 (3.1%)	525 (0.75%)	4.1 (2.9–5.6)
Congenital malformations	61 (5.0%)	1,987 (2.8%)	1.7 (1.3–2.2)
Respiratory distress syndrome§	202 (17.1%)	ND	—
Jaundice‖	215 (18.1%)	ND	—

Data are means ± SD or *n* (%). *Blood pressure ≥140/90 mmHg and proteinuria. The frequency in the background population is 2.6% (other data source, see text); †before 37 completed weeks of gestation; ‡birth weight ≥90th centile. The expected frequency in the background population is 10%, but exact numbers are not available; §use of continuous positive airway pressure for >1 h postpartum; ‖use of phototherapy. ND, no data.

the reporting of cases from the centers was 75–93% evaluated by alternative local data sources. In one region (Northern Jutland County), data were cross-checked with a hospital discharge registry and an insulin-prescription registry, yielding a coverage of 75%. In the Odense University Hospital area, local registration of pregnant women with diabetes (type 1, type 2, and gestational diabetes) was performed by the head of the obstetric department, and 93% of women with type 1 diabetes were found in both registries. Maternal characteristics and pregnancy outcome showed no differential selection, suggesting that the results from the registry can be generalized despite incomplete data ascertainment. No significant variation in data collection was present over the years. Data on the background population were based on 70,089 deliveries recorded by the Danish Health Board in 1995 (8). Statistics were performed with STATA 7.0 (Stata Corporation, College Station, TX). Data are given as standard deviation and mean, median and interquartile range, or numbers and percent. Mann-Whitney *U* test or χ^2 test was used for comparing pregnancies with and without serious outcomes. Logistic regression analysis was performed to determine predictors for perinatal mortality and/or congenital malformations. *P* values <0.05 were considered statistically significant.

Perinatal mortality was defined as stillbirth (intrauterine death after 24 weeks of gestation) or death during the first 7 days of life. Congenital malformations were assessed during hospital stay, whereas malformations diagnosed on a subsequent examination were not registered. Major congenital malformations were those responsible for death, causing a significant future handicap, or requiring major surgery, whereas minor congenital malformations comprise the remainder (9). Macrosomia was defined as birth weight ≥4,500 g or birth weight ≥90th percentile for a Danish standard population (10), and preterm delivery was delivery before 37 completed weeks. Preeclampsia was defined as blood pressure >140/90 mmHg and proteinuria 2+ on a urine protein test strip (equal to 1.0 g/l).

RESULTS — Data were reported on 1,218 consecutive pregnancies in 990 women during the study period. Twenty-eight were twin pregnancies. Patients had a mean age of 28.8 years and mean BMI of 22.9 kg/m^2 (not different from the background population), duration of diabetes was 12 years (5–19), and the time for admission to the center was 9 gestational weeks (8–11) (median and interquartile range). Information of preconceptional guidance was recorded in 1,153 women, and 669 (58%) had received guidance. At the time of admission, 381 (34%) performed daily blood glucose monitoring, whereas 53, 62, and 65% did that in the first, second, and third trimester. HbA_{1c} values decreased with advancing pregnancy: 0–3 months before conception (7.6% [6.8–8.6]); first trimester (7.3% [6.6–8.2]); second trimester (6.6% [6.0–8.3]); and third trimester (6.7% [6.2–7.4]) (median and interquartile range). Approximately 95% of the women were treated with insulin four times a day (basal/bolus regime) before and during pregnancy. None of the women used insulin pumps.

Obstetric and fetal characteristics for patients and the reference population are shown in Table 1. Infants of women with type 1 diabetes were delivered earlier, and rates of caesarean section, macrosomia, stillbirth, perinatal mortality, and congenital malformations were higher than in normal newborns. Thirty-two (52%) of the detected congenital malformations were defined as major.

Among the 680 caesarean sections, 373 (55%) were performed electively. A total of 255 (48%) of the preterm deliveries were based on obstetrical or medical indications and followed by either induction of labor or elective caesarean section. Eighteen percent had preeclampsia versus 2.6% in the background population (data from the National Danish Patient Registry 1998–2000, Marianne Johansen, personal communication, Copenhagen).

Table 2 gives maternal characteristics in pregnancies with and without serious adverse outcomes (perinatal mortality and/or congenital malformations). Adverse outcomes were associated with significantly higher HbA_{1c} values before and during pregnancy and with lower rates of preconceptional guidance and daily blood glucose monitoring before conception. Mothers with severe adverse outcomes had lower preconceptional BMI. The congenital malformations affected

Table 2—*Maternal characteristics in pregnancies with serious adverse outcomes (perinatal death and/or congenital malformations) versus other pregnancies*

	Serious adverse outcome	Others	*P*
n	93	1,125	
Age (years)	28 (25–31)	29 (26–32)	0.49
Preconceptional BMI (kg/m^2)	22.1 (19.4–24.2)	23.0 (21.4–25.3)	0.01
Diabetes duration (years)	12 (6–18)	12 (5–19)	0.75
Daily blood glucose monitoring at conception	18 (22.5%)	363 (34.6%)	0.019
Preconceptional guidance	38 (42.7%)	631 (59.2%)	0.002
HbA_{1c} 0–3 months prior to conception (%)	8.0 (7.3–9.1)	7.6 (6.8–8.5)	0.005
HbA_{1c} during first trimester (%)	7.6 (6.6–8.6)	7.3 (6.6–8.1)	0.037
HbA_{1c} during second trimester (%)	6.9 (6.2–8.0)	6.6 (6.0–7.3)	0.012
HbA_{1c} during third trimester (%)	7.1 (6.5–7.9)	6.7 (6.2–7.4)	<0.001
Retinopathy*	5 (5.8%)	78 (7.3%)	0.58
Nephropathy†	8 (9.0%)	70 (6.4%)	0.34
Hypertension‡	6 (6.7%)	53 (4.8%)	0.45
Pre-eclampsia§	15 (18.1%)	205 (18.1%)	1.0
Large for gestational age infant‖	48 (57.1%)	713 (62.9%)	0.30

Data are median (interquartile range) or *n* (%). For some of the variables, the total number is <1,218 due to missing values. *Proliferative retinopathy; †nephropathy (urine albumin excretion >300 mg/24 h or >200 μg/min); ‡hypertension (pharmacological treatment) before pregnancy and/or during first trimester; §blood pressure ≥140/90 mmHg and proteinuria; ‖birth weight ≥90th centile.

the following organ systems: 44% cardiovascular, 18% musculoskeletal, 13% urinary, 7% central nervous, and 18% others. The neonatal deaths were primarily associated with preterm delivery (30.0 weeks [26.5–33.1] median [interquartile range]); 3 of the 12 infants had major congenital malformations. Logistic regression analysis was performed entering only data from the first pregnancy for each woman in the study (index pregnancy, $n = 990$). In univariate analysis, significant predictors ($P < 0.05$) for serious adverse outcomes were absence of daily monitoring of blood glucose before conception ($P = 0.023$), HbA_{1c} 0–3 months before conception ($P = 0.029$), second trimester HbA_{1c} (0.043), and third trimester HbA_{1c} ($P < 0.01$). Absence of preconceptional guidance and first trimester HbA_{1c} tended to be associated with perinatal mortality/congenital malformations ($P = 0.062$ and $P = 0.13$, respectively). When entering the four HbA_{1c} values one at a time in a multivariate model with preconceptional guidance and daily blood glucose monitoring, only third-trimester HbA_{1c} remained significantly associated with serious adverse outcome.

Women who performed daily blood glucose self-monitoring at any time during pregnancy had lower HbA_{1c} values (mean ± SD) than women who did not measure daily: preconceptional HbA_{1c} 7.2 ± 1.1 vs. 7.8 ± 1.5% ($P < 0.0001$); second trimester HbA_{1c} 6.7 ± 1.0% vs. 7.1 ± 1.2% ($P < 0.0001$); and third trimester HbA_{1c} 6.7 ± 0.9 vs. 7.1 ± 1.1% ($P < 0.0001$). Likewise, daily self-monitoring was negatively associated with serious adverse outcomes in univariate analyses: preconceptional 4.6 vs. 7.6% ($P = 0.03$); first trimester 5.3 vs. 8.3% ($P = 0.037$); second trimester 5.7 vs. 8.3% ($P = 0.087$); and third trimester 5.3 vs. 8.1% ($P = 0.061$).

CONCLUSIONS — To our knowledge, this is the largest prospective population-based study of unselected pregnant women with type 1 diabetes. It could be argued that a number of women might have type 2 diabetes, as no data were recorded on C-peptide or islet cell immune markers. However, women entering the study were all judged as having type 1 diabetes by their caretakers and were on insulin treatment before conception, the majority were normal weight, and the mean diabetes duration was 12 years.

As in other series from the 1990s (2–7,11,12), we found increased rates of obstetric complications, stillbirth, perinatal mortality, congenital malformations, and macrosomia compared with the background population. There was a striking increased risk for preterm delivery (more than one-half of them spontaneous), which is an important risk factor for infant morbidity.

The stillbirth rate in our study (2.1%) was comparable with the rate of 1.9% in Scotland (5) and 2.0% in Newcastle-upon-Tyne, U.K. (3). Perinatal mortality was 3.1%, which was also in the same magnitude as in the national studies from Holland and Scotland (5,6) (3.2 and 2.8%, respectively). In two consecutive cohorts in the Liverpool area, U.K. (2,11), and in one cohort from Newcastle-upon-Tyne (3), perinatal mortality tended to be higher (3.6–4.3 and 4.8%, respectively), but the difference was not statistically significant.

The congenital malformation rates differed substantially, with frequencies of 7.9–9.7% in the studies from Holland and England and rates of 4.2–6.1% in the Scandinavian and Scottish series. The relative risk for congenital malformations in the present study was lower: 1.7 among offspring of diabetic women compared with offspring of normal women. Malformations were assessed during the first week of life in offspring of diabetic mothers, whereas congenital malformations in the background population were reported to a central registry after the first year of life. This would tend to underestimate both the congenital malformation rate in diabetic women and the relative risk compared with the background population. In contrast to most previous studies, we also included pregnancies terminated before 24 weeks due to ultrasound-diagnosed congenital malformations.

For decades, management of pregnant women with diabetes has focused on the importance of optimizing glycemic

control before and during pregnancy. In Denmark, health care is free with equal access for all citizens, and young women with diabetes are offered regular visits to diabetologists. Therefore, it was disappointing that only one-third of the women performed daily home glucose monitoring at the time of conception and that nearly one-half of them did not receive prepregnancy guidance. Moreover, our study clearly underlines that women using home blood glucose monitoring had better glycemic control throughout pregnancy as well as a better pregnancy outcome.

HbA_{1c} is a crude measure of glucose control during pregnancy, as it reflects changes in glucose over several weeks, and therefore results of glucose profiles during home monitoring might have added important information. Unfortunately, these data were not reported to the central registry. The clinical decisions during pregnancy were, of course, also based on glucose profiles and not only on HbA_{1c} values.

Our study confirms that poor metabolic control before and during pregnancy is associated with perinatal mortality and congenital malformations. Furthermore, these outcomes were predated by inadequate maternal self-care (home monitoring of blood glucose) and professional care (preconceptional guidance). Finally, women with adverse pregnancy outcome seemed to have slightly more hypertension and overt diabetic nephropathy at conception, but this did not reach statistical significance. In the multivariate analysis, only third-trimester HbA_{1c} remained a significant predictor. However, as perinatal mortality and congenital malformations are rare complications, sufficient statistical power would require an even larger study population.

HbA_{1c} level decreased during pregnancy but was still higher than the reference interval for individuals without diabetes. This decrease might be due to the intensified insulin regimen; however, recent Danish investigations have shown that HbA_{1c} values also decrease during pregnancy in normal women and that third-trimester reference interval is as low as 4.4–5.6% (13). Thus, many of our patients were far from optimally controlled, and consequently, we should aim at even tighter glycemic control. However, the price could be more hypoglycemic episodes. As shown by Evers et al. (14), the risk is increased during early pregnancy and in women with a history of severe hypoglycemia, high daily insulin dose, and long duration of diabetes. With this knowledge and an increased patient compliance with respect to home blood glucose measuring, it should be possible to tailor individual treatment regimens.

Like other investigators, we found an increased risk of macrosomia, despite earlier delivery in women with type 1 diabetes. In the Dutch population (15), one-half of the diabetic women delivered macrosomic infants (birth weight ≥90th percentile) with a mean third-trimester HbA_{1c} in this group of 6.4% (normal nonpregnant reference value 4.0–6.0%). The authors concluded that macrosomia occurred despite apparent good glycemic control. According to the above-mentioned reference intervals for normal pregnant women, it could be argued that this is far from normal physiologic glucose levels.

The goals of the St. Vincent declaration have not yet been obtained. A nationwide Swedish study (1983–1985) reported congenital malformation rates similar to the general population and moderately increased risk of macrosomia in diabetic women (16), whereas data from the Swedish Medical Birth Registry (1991–1996) showed an increase in macrosomia and a threefold risk of congenital malformations in diabetic women (12). An audit from Northern Ireland reported data from 978 pregnancies in diabetic mothers during 1985–1995 (17). Perinatal mortality rates were higher in women who were managed in a local maternity unit compared with a regional center (3.6 vs. 2.9%). Women who registered for prenatal care locally and were transferred to the regional center midpregnancy had a much higher perinatal mortality of 7.5%. The results underline the importance of centralization and early referral of pregnant women with diabetes. Analyses of unselected populations are necessary to set realistic goals for pregnancy outcome, as single-center studies from highly specialized hospitals tend to be overly optimistic.

In accordance with the Swedish data, the study from Northern Ireland did not demonstrate any improvements in pregnancy outcome over time. The reason for this is not clear. It could be speculated that more diabetic women with complications become pregnant due to improved treatment of infertility. Furthermore, the maternal age of the first pregnancy is increasing (8), which is a fact that might have more severe implications for women with diabetes.

Our data suggest that glycemic control, self-care, and education of the patient still need to be improved significantly and that adequate control using daily glucose monitoring in all patients is a crucial step toward reaching the goals of the St. Vincent Declaration. Future research should focus on tools for better preconceptional care, development of new methods like continuous glucose monitoring, more efficient insulin regimens, and assessment of risk indicators for certain adverse outcomes. This would make it possible to individualize treatment and target health care resources to risk groups.

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