Obstetric and Perinatal Outcomes in Type 1 Diabetic Pregnancies

A large, population-based study

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OBJECTIVE — To perform comparative analyses of obstetric and perinatal outcomes between type 1 diabetic pregnancies and the general obstetric population in Sweden between 1991 and 2003.

RESEARCH DESIGN AND METHODS — This was a population-based study. Data were obtained from the Medical Birth Registry, covering >98% of all pregnancies in Sweden. A total of 5,089 type 1 diabetic pregnancies and 1,260,207 control pregnancies were included. Odds ratios (ORs) were adjusted for group differences in maternal age, parity, BMI, chronic hypertensive disease, smoking habits, and ethnicity.

RESULTS — In type 1 diabetes, preeclampsia was significantly more frequent (OR 4.47 [3.77–5.31]) as was delivery by cesarean section (5.31 [4.97–5.69]) compared with results for the general population. Stillbirth (3.34 [2.46–4.55]), perinatal mortality (3.29 [2.50–4.33]), and major malformations (2.50 [2.13–2.94]) were more common in type 1 diabetic than in control pregnancies. The risk of very preterm birth (<32 gestational weeks) was also higher among type 1 diabetic women (3.08 [2.45–3.87]). The incidence of fetal macrosomia (birth weight ≥2 SD above the mean) was increased in the diabetic group (11.45 [10.61–12.36]).

CONCLUSIONS — Type 1 diabetes in pregnancy is still associated with considerably increased rates of adverse obstetric and perinatal outcomes. The eightfold increased risk for fetal macrosomia in type 1 diabetic pregnancies is unexpected and warrants further investigation.

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Type 1 diabetes in pregnancy is associated with increased risks of maternal and fetal complications. In a Swedish study from 1982 to 1985, the perinatal mortality (3.1%) and stillbirth rates (2.1%) were 4–5 times those of the general population (1). Since then and after the introduction of tight glycemic control, outcomes of type 1 diabetic pregnancies are considered to have improved significantly. However, objective and unanimous estimates of improvement in care are difficult to find. More recent studies on type 1 diabetic pregnancies have reported various results: stillbirth and perinatal mortality were still significantly increased in some studies (2–6), the risk for major malformations varied from 2 to 10 times normal (2,4,6), and the incidence of fetal macrosomia remained markedly increased, despite apparently good metabolic control with A1C levels close to the normal range (7,8). Accordingly, the aim of the St. Vincent Declaration from 1989 (9), i.e., to abolish the overt risks associated with pregnancy in women with type 1 diabetes by the end of the last century, has not been achieved. There is no clear explanation for the wide variation in perinatal outcomes for diabetic pregnancies. Differences in organization of health care, socioeconomic factors, maternal characteristics, and patient compliance could account for some of the observed differences. More favorable results reported from centers of excellence may reflect some selection bias. Given the relatively low incidence of congenital malformations and perinatal mortality, large studies are required for accurate risk estimates, and variations in outcomes for type 1 diabetic pregnancies may be associated not only with diabetes but also with other risk factor variations in the general obstetric population.

The primary aim of this study was to provide solid evidence for obstetric and perinatal outcomes in type 1 diabetic pregnancies. We compared outcomes in >5,000 type 1 diabetic pregnancies with those in the general obstetric population in Sweden over a period of 13 years (1991–2003). The large numbers included in the study offered a possibility to obtain objective and precise estimates of complications in diabetic pregnancies and to adjust for potential confounders. To facilitate interpretation of our results in relation to organization of care and change over time, we compared hospitals in relation to the number of type 1 diabetic pregnancies managed per year and subgrouped outcomes in relation to calendar period of birth.

RESEARCH DESIGN AND METHODS

— This prospective study was based on information from the Swedish Medical Birth Registry (MBR) between 1991 and 2003. The MBR is regularly evaluated by the Swedish National Board of Health, and in the latest evaluation, it was found to capture >98% of all pregnancies in Sweden. The quality of data has also been found to be reliable (10). This study included all type 1 diabetic pregnancies, and pregnant women without a diagnosis of type 1 diabetes served as control subjects. In both groups, only singleton births were included.

We used the ICD-9 and ICD-10. Since 1991, pregestational diabetes can be separated from gestational diabetes mellitus (GDM) by ICD-9, and since 1997, type 1 diabetes, type 2 diabetes, and GDM can be separated from each other by ICD-10. The Swedish rate of type

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2 diabetes in pregnancy is ≤5% (U.H., personal communication). Therefore, the overall contribution from any type 2 diabetic woman included in the diabetic population during the first 6 years of the study period was considered small and insignificant.

In Sweden, pregnancy care is standardized and free of charge. Virtually all pregnant women comply with seven to nine antenatal visits (one to two to a physician and the remainder to a midwife). In diabetic pregnancies, the number of antenatal visits is increased. Of all pregnant women, 97% have an ultrasound examination at 17–18 postmenstrual weeks to determine gestational age.

At the first antenatal visit, the woman was interviewed about her medical history, previous births, and complications during the previous pregnancy, delivery, and neonatal period. Anthropometric data and smoking habits were recorded. Pregnancy and delivery data were prospectively entered into the MBR, which also included neonatal anthropometry and diagnoses. For this purpose, standardized individual obstetric and pediatric forms were used. Maternal characteristics were age, parity, prepregnancy weight, height, smoking habits, and place of birth (i.e., whether the mother was born in the Nordic countries [Sweden, Finland, Denmark, Norway, or Iceland] or elsewhere). These variables, except ethnicity, were all collected from the MBR. Country of birth was established by linking the MBR to the Civil Registration. Maternal prepregnancy BMI was calculated (weight in kilograms divided by the square of height in meters). We defined smoking categories as no smoking, smoking <10 cigarettes per day, or smoking ≥10 cigarettes per day. Maternal complications during pregnancy and delivery and fetal and neonatal complications were classified according to ICD-9 and -10. All diagnoses were made by a physician at the time of hospital discharge, and copies of obstetric and pediatric records were forwarded to the MBR. Chronic hypertensive disease (ICD-9 code 401 or 642 A; ICD-10 code I10 or O10.0) was defined as blood pressure ≥140/90 mmHg diagnosed before pregnancy or before 20 weeks of gestation. Pregnancy-induced hypertension (PIH) was defined as resting blood pressure ≥140/90 mmHg in the second half of pregnancy (ICD-9 code 642 D3; ICD-10 code O13). Preeclampsia was defined as PIH and proteinuria of ≥0.3 g/day or ≥1+ on a urine dipstick (ICD-9 code 642 E or 642 F; ICD-10 code O14.0, O14.1, or O15). Mild preeclampsia was defined as diastolic blood pressure from 90 to 109 mmHg combined with proteinuria of <5 g/day or 1–2+ on a urine dipstick (ICD-9 code 642E; ICD 10 code O14.0). Severe preeclampsia was defined as preeclampsia with either a diastolic blood pressure ≥110 mmHg or proteinuria ≥5 g/day or both (ICD-9 code 642 F; ICD-10 code O14.1 or O15). Preterm birth was defined as delivery before 37 gestational weeks and very preterm birth as delivery before 32 weeks. During the study period, stillbirth was defined in Sweden as intrauterine death occurring after 28 weeks of gestation.

Perinatal death was defined as the combined rate of stillbirth and mortality within the first week of life. Neonatal mortality was defined as death within the first 7 days of life (early neonatal death) and within the first 28 days of life. Fetal distress was present whenever vacuum extraction or cesarean section was performed as a result of suspected or manifest fetal hypoxia. Large for gestational age (LGA) and small for gestational age (SGA) were defined as birth weights ≥2 SD above or below the mean for normal fetal growth according to Swedish reference data, respectively (11). The corresponding percentile limits for LGA and SGA are ≥97.5 and ≤2.5 percentiles, respectively. Apgar scores between 0 and 3 at 5 min of postnatal age were recorded as well as brachial plexus injury in vaginally delivered infants. Neonatal respiratory disorders were classified according to Hjalmarson (12). Transient tachypnea, respiratory distress, and other diagnoses of respiratory disturbances (ICD-9 codes 769 and 770G; ICD-10 all codes starting with P 22, P 24, P 25, and P 26) were included in the analysis. A malformation was classified by the MBR as major if it was fatal or potentially life-threatening or if it was likely to lead to serious handicap or major cosmetic defect if not surgically corrected. We compared the outcomes between hospitals managing <10 (total number of patients 2,190), 10–19 (n = 1,910), and >19 (n = 989) type 1 diabetic pregnancies per year. We also categorized the study period into the first 7 years (1991–1997) and the next 6 years (1998–2003).

Statistical methods

Means ± SDs were calculated. Student t test and the χ^2 test were used for comparison of group means and proportions. Logistic regression was used to evaluate any association between maternal type 1 diabetes and outcomes. In multivariate analyses, the point estimates for outcomes were adjusted for maternal age, BMI, parity, chronic hypertensive disorder, smoking habits, and ethnicity. Because of missing data on prepregnancy BMI, multivariate analyses were limited to 954,292 mothers. All statistical analyses were performed using SPSS (version 15.0).

RESULTS

— In total, 5,089 pregnant women with and 1,260,207 pregnant women without type 1 diabetes were included.

Maternal characteristics

Women with type 1 diabetes more often had prepregnancy hypertension, were of Nordic origin, and had higher BMI than the general obstetric population. Maternal age, parity, and smoking habits showed minor but statistically significant differences between women with diabetes and control subjects (Table 1).

Pregnancy complications

The risks for PIH and preeclampsia, fetal distress and fetal loss, and instrumental delivery and cesarean section were all increased in the diabetic cohort, also after adjustment for potential confounders (Tables 2 and 3). In the diabetic cohort, the majority of stillbirths (58 of 69) occurred between 34 and 40 gestational weeks. In vaginal deliveries, shoulder dystocia occurred in 13.7% of infants delivered by diabetic mothers compared with 0.2% of control infants ($P < 0.001$), which corresponds to an adjusted odds ratio (OR) of 11.08 (95% CI 8.22–14.93).

Fetal growth

Infants of diabetic mothers were born at a lower gestational age (mean 267 vs. 278 days, $P < 0.001$) than control infants. Despite this, birth weights (3,684 g vs. 3,551 g, $P < 0.001$) were higher in infants of diabetic mothers. Birth weights were close to normally distributed in the diabetic cohort with only a minor difference between the mean and median birth weight. After correction for gestational age and sex, birth weights were increased in the diabetic group: 31% of the infants born to type 1 diabetic mothers were LGA compared with 3.6% of infants born to mothers in the general population. Birth weights ≥4.5 and 5 kg, respectively, were significantly more common in the diabetic group (12.6 and 2.7%) than among

Table 1—*Maternal characteristics in type 1 diabetes and the general obstetric population in Sweden 1991–2003*

	Type 1 diabetes	Control
n	5,089	1,260,207
Nordic origin (%)	92.6	86.8
Maternal age (years)	29.6 ± 5.1	29.0 ± 5.1
Primapara (%)	44.5	42.4
Height (cm)	166 ± 6.3	166 ± 6.2
Prepregnancy weight (kg)	71.4 ± 13.4	66.5 ± 12.1
Prepregnancy BMI (kg/m^2)	25.9 ± 4.6	24.0 ± 4.1
Chronic hypertensive disease (%)	2.1	0.24
No smoking in pregnancy (%)	82.0	83.8
Smoking		
<10 cigarettes /day (%)	10.9	10.6
≥10 cigarettes/day (%)	7.1	5.6

Data are means ± SD or proportions in %. With the exception of maternal height, all differences between type 1 diabetic and control women are statistically significant with $P < 0.001$ (Student *t* test or χ^2 test).

control infants (3.9 and 0.5%, $P < 0.0001$). The adjusted OR for SGA was significantly lower in the type 1 diabetic group than in the control group (Table 3).

Malformations

In the diabetic group, there was a twofold increase in the incidence of major malformations (Table 3). Major malformations were the leading cause of neonatal death (10 of 36) in the diabetic cohort.

Neonatal mortality and morbidity

Perinatal and neonatal mortalities were significantly increased in diabetic pregnancies. Low Apgar scores (0–3) at 5 min of postnatal age, Erb palsy, and respiratory distress were all significantly and much more common in infants of diabetic mothers (Table 3).

Outcomes in relation to hospital size

Fetal distress and transient tachypnea were more common in larger hospitals caring for >19 type 1 diabetic pregnant women per year. Except from these two outcomes, there were no significant differences in obstetric and perinatal outcome among hospitals of different size.

Outcomes in relation to calendar period of birth

The incidence of LGA increased in the diabetic group from 27.6% in the first to 35.0% in the second period of the study ($P < 0.001$). The proportion of LGA infants increased significantly in the general obstetric population also, from 3.38% in the first to 3.77% in the last study period ($P < 0.001$).

Over time, the proportion of women with BMI ≥30 kg/m^2 increased in both groups. In the first study period, 13.2% of type 1 diabetic women were obese compared with 18.4% during the second period ($P < 0.001$). The corresponding figures for control women were 7.3% (period 1) and 11.3% (period 2).

Table 2—*Pregnancy complications and mode of delivery in type 1 diabetic and control pregnancies*

	Proportions (%)		OR (95% CI) for group differences	
Outcome variable	Type 1 diabetes	Nondiabetes	Crude	Adjusted
PIH	1.6	0.87	1.93 (1.50–2.49)	1.53 (1.18–1.99)
Preeclampsia, mild	9.7	2.0	5.37 (4.81–6.00)	4.30 (3.83–4.83)
Preeclampsia, severe	4.3	0.8	5.58 (4.75–6.57)	4.47 (3.77–5.31)
Cesarean section	46	12	5.85 (5.49–6.25)	5.31 (4.97–5.69)
Vacuum extraction/forceps	9.6	6.6	1.48 (1.33–1.66)	1.41 (1.25–1.58)

Data are proportions or OR (95% CI). n = 5,089 for diabetic pregnancies; n = 1,260,207 for control pregnancies. Adjusted OR, OR adjusted for group differences in maternal age, BMI, parity, chronic hypertensive disorder, smoking habits, and ethnicity.

CONCLUSIONS — This study showed that pregnant type 1 diabetic women still have markedly elevated incidences of obstetric and fetal complications such as preeclampsia, prematurity, malformations, perinatal mortality, and neonatal morbidity. The risk for a LGA infant was particularly increased among women with diabetes.

The strength of the present study is the population-based cohort, including both stillborn and live-born infants. Population-based data are essential for assessing solid estimates of complication rates, for planning of health care, for patient counseling, and for comparisons between countries and populations. The large numbers of patients allowed for detailed risk assessments, also including rare complications such as perinatal mortality and malformations. Potential confounding by other risk factors, such as age, parity, BMI, and chronic hypertensive disease, could be controlled for.

We cannot exclude the possibility that during the first study period some type 2 diabetic patients could have been included in the study population because the ICD-9 codes just differ between pregestational diabetes and GDM. However the rate of type 2 diabetes in pregnancy is low in Sweden. If anything, the small fraction of type 2 diabetic women that may have been included most likely contributed to a dilution of the complication rates observed in type 1 diabetic women. Accordingly, this potential misclassification bias does not invalidate our findings.

One limitation is that the MBR does not contain data on duration of diabetes, prevalence of preexisting microangiopathy, or glycemic control during pregnancy. Another limitation is the lack of data regarding the number of induced abortions due to malformations. The present analysis confirms the elevated risks for preeclampsia and PIH in women with type 1 diabetes. This is in accordance with findings in other comparable studies (4,13). The precise explanation for this finding is not known. However, chronic hypertensive disease, nephropathy, and poor glycemic control are probably contributing factors (14–16).

Stillbirths in diabetic pregnancies (1.5%) were 5 times those in the background population. Although markedly reduced compared with data from 40 years ago (17), excess risk for stillbirth is still seen in diabetic pregnancies in agreement with contemporary studies (4,13,18). The underlying mechanisms

Table 3—*Fetal and neonatal complications in type 1 diabetic pregnancies and the general obstetric population*

Outcome variable	Proportions (% if not indicated otherwise)		OR (95% CI) for group differences	
	Type 1 diabetes	Control	Crude	Adjusted
Stillbirth	1.5	0.3	4.04 (3.02–5.40)	3.34 (2.46–4.55)
Fetal distress	14	6.2	2.45 (2.24–2.69)	2.34 (2.12–2.58)
Perinatal mortality (‰)	20	4.8	4.02 (3.11–5.20)	3.29 (2.50–4.33)
Neonatal mortality, 0–7 days (‰)	5.1	1.8	2.91 (1.97–4.28)	3.05 (1.68–5.55)
Neonatal mortality, 0–28 days (‰)	7.0	2.2	3.08 (2.02–4.70)	2.67 (1.72–4.16)
Birth <37 weeks gestational age	21	5.1	5.27 (4.88–5.71)	4.86 (4.47–5.28)
Birth <32 weeks gestational age	2.3	0.7	3.58 (2.89–4.44)	3.08 (2.45–3.87)
LGA	31	3.6	12.2 (11.4–13.1)	11.4 (10.6–12.4)
SGA	2.3	2.5	0.80 (0.63–1.02)	0.71 (0.55–0.91)
Major malformations	4.7	1.8	2.70 (2.37–3.08)	2.50 (2.13–2.94)
Apgar score <7 at 5 min	3.1	1.1	2.98 (2.54–3.50)	2.60 (2.14–3.17)
Apgar score <4 at 5 min	0.80	0.30	2.60 (1.79–3.78)	2.39 (1.64–3.51)
Erb palsy*	2.1	0.25	7.91 (5.77–10.8)	6.69 (4.81–9.31)
Respiratory distress syndrome	1.0	0.20	4.88 (3.51–6.81)	4.65 (2.20–9.84)
Respiratory disorders	9.5	2.6	4.02 (3.67–4.42)	3.42 (3.04–3.85)

Data are proportions or OR (95% CI). Adjusted OR, OR adjusted for group differences in maternal age, BMI, parity, chronic hypertensive disorder, smoking habits, and ethnicity. *Vaginal deliveries only.

for stillbirth in diabetic pregnancies are not fully understood. Maternal and fetal hyperglycemia are associated with chronic fetal hypoxia, as indicated by a correlation between the concentration of erythropoietin in amniotic fluid and antenatal glycemic control (19). Lauenborg et al. (20) reported 25 cases of stillbirth in type 1 diabetic pregnancies and found no cause of death other than poor maternal glycemic control in 9 cases. Similarly, Hanson and Persson (1) recorded significantly higher A1C levels in the last trimester in 5 of 10 stillbirths in diabetic mothers. Fetal hypoxia may also explain why fetal distress as an indication for instrumental delivery or cesarean section was nearly 3 times more common in diabetic pregnancies compared with control pregnancies.

Major malformations occurred 2–3 times more often in the diabetic group. This occurrence is comparable to some (4,6) but not all reports. Even higher rates of major malformations compared with those in the control group have been reported from the U.K. (2). Differences in metabolic control (21), in definitions of major malformation, in the number of early induced abortions, and in intrapartum deaths may contribute to this discrepancy. The malformation rate should also be interpreted in view of the fact that in Sweden, there is no fortification of food with folic acid. Prepregnancy counseling to women with type 1 diabetes includes the recommendation for folic acid supplementation, but we have no data regarding compliance with this recommendation or folic acid intake before conception.

Rates of instrumental delivery (9.6%) and cesarean section (46%) were much higher in the diabetic group. This finding is in agreement with other reports (4). Studies on type 1 diabetic pregnancies from Finland and Denmark reported even higher rates of cesarean sections (63.5 and 55.9%, respectively) (5,13). The lower cesarean section rate in Sweden could be explained partly by a more expectative policy, where spontaneous initiation of delivery is encouraged. This suggestion is supported by higher numbers of preterm deliveries reported from Finland and Denmark: 30 and 42%, respectively (5,13), vs. 22% in our study. Many of the preterm deliveries in other studies were performed before the start of or after induction of labor (13). Perinatal mortality in type 1 diabetic pregnancies in Sweden has decreased from 3.1% in 1982–1985 (1) to 2.0% in the present study, and it is in the lower range of previously recorded rates, varying from 1.3 to 6.6% (4–6,13,18,22). Nevertheless, perinatal mortality in type 1 diabetic women exceeds that in control women by 4 times, mainly because of the increased risk for stillbirth. To a lesser extent, neonatal mortality rates were also increased in infants of diabetic women, most likely because of their higher incidence of malformations, preterm delivery, and birth asphyxia. An unexpected observation was the markedly increased incidence of fetal macrosomia in diabetic pregnancies. The incidence of LGA (31%) was >8 times that of the control group. In comparison with Swedish data from 1982–1985, the incidence of LGA has increased 11% in absolute values and ~50% relatively (1). The risk for LGA increased significantly over time in the present study. High rates of macrosomia have also been reported from Holland (28.4%) and Finland (34.7%) (4,5). It is unlikely that the increased LGA incidence is a consequence of deterioration in metabolic control, as both the stillbirth and major malformation rates have declined. One could speculate that a contributing factor to the increasing incidence of LGA is a decreasing rate of microangiopathy (23). Interactions with other determinants of birth weight, such as prepregnancy BMI, may also contribute to this finding. However, the excess risk for an LGA infant remained high (OR 11, 45) even after adjustment for maternal BMI.

Very preterm delivery was 3 times that of the control deliveries, contributing to the higher incidence of neonatal morbidity such as respiratory distress syndrome in the offspring of diabetic mothers. We also found an 8 times higher incidence of Erb palsy in the offspring of diabetic mothers than in the offspring of normal mothers. It is well recognized that infants of mothers with diabetes have a smaller head-to-shoulder ratio. The disproportionate body constitution increases the propensity of shoulder dystocia and Erb palsy, and the risk of these complications also increases with larger size of the baby. There is no clear explanation for the variation in obstetric and perinatal outcomes of type 1 diabetic pregnancies among different countries. The discrepancy in reported rates of complications could result in part from differences in organization of health care, socioeconomic factors, and patient compliance. In Sweden, antenatal care of pregnant women with diabetes is usually preformed in hospitals. The population is scattered over a large geographical area, which precludes centralization of care to regional centers. Almost half of the pregnant women with diabetes attended small clinics caring for <10 pregnant type 1 di-

abetic women per year. The care is generally provided by multidisciplinary teams with a special interest in diabetes. All patients are given insulin and equipment for insulin administration, as well as equipment for home monitoring of blood glucose. The importance of prepregnancy planning is emphasized, starting initially at the pediatric clinic. National recommendations concerning standardization of care are available. Before and during the study period, diabetologists provided health care personnel with information and guidelines for medical management of pregnant diabetic women. This work seems to have been successful as major outcomes did not vary in relation to hospital size. Similar experience has been reported from Finland where decentralization of care for diabetic patients did not significantly increase the number of adverse pregnancy outcomes (5). However, we cannot exclude the possibility that the higher incidence of fetal distress and transient tachypnea observed in larger hospitals caring for >19 pregnant type 1 diabetic women per year reflected a selection with women having the most complicated pregnancies being transferred to the larger hospitals. Given such selection, smaller hospitals would be expected to have better results. The number of preterm births and cases of severe preeclampsia did not differ between large and smaller clinics, but without a more detailed analysis of the case mix of diabetic women in different hospitals, the issue of whether centralization occurred has to be left open.

In summary, the present study demonstrates that incidence of obstetric and perinatal complications is still high in the diabetic pregnancy. An intriguing finding is the high incidence of fetal macrosomia and the fact that the incidence is increasing over time. The etiology behind the increased risk of fetal death and fetal macrosomia in the type 1 diabetic pregnancy is not fully understood and warrants further investigation.

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