Differing Causes of Pregnancy Loss in Type 1 and Type 2 Diabetes

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OBJECTIVE — Women with type 2 and type 1 diabetes have differing risk factors for pregnancy loss. We compared the rates and causes of pregnancy loss in women with type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS — We utilized prospectively collected data on all pregnancies in a 20-year period (1986–2005) from a single center with a high prevalence of type 2 diabetes. Pregnancy losses included terminations for medical reasons and deaths up to 1 month postpartum but not spontaneous pregnancy losses <20 weeks' gestation.

RESULTS — There were 870 pregnancies in women with known diabetes (330 with type 1 and 540 with type 2 diabetes) and 325 in women with diabetes diagnosed in pregnancy but persisting postpartum (97% type 2 diabetes). The rate of pregnancy loss was similar in type 1 and type 2 diabetes (2.6 vs. 3.7%, $P = 0.39$), but the causes of pregnancy loss differed. In type 1 diabetes >75% were attributable to major congenital anomalies or prematurity; in type 2 diabetes >75% were attributable to stillbirth or chorioamnionitis ($P = 0.017$). Women with type 2 and type 1 diabetes had similar A1C at presentation and near term, but the former were older ($P < 0.001$) and more obese ($P < 0.0001$).

CONCLUSIONS — There are significant differences in the main causes of pregnancy loss in women with type 1 and type 2 diabetes. The higher rates of stillbirth in women with type 2 diabetes, suggest that other features, such as obesity, contribute significantly to pregnancy losses.

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Before the discovery of insulin, a woman with type 1 diabetes had almost no chance of successful delivery of a healthy baby. With the advent of insulin treatment, pregnancy losses continued to be high, predominantly through stillbirth, but neonatal deaths due to congenital malformation, birth trauma, hypoglycemia, and respiratory distress syndrome all took their toll (1). Substantial improvement in the rates of perinatal mortality followed the development of centralized care and regimens focused on achieving strict glycemic control and ensuring early delivery (2,3). Several centers have reported stillbirth rates in women with type 1 diabetes that are comparable to those in nondiabetic women (4–7). Pregnancy losses due to congenital anomalies (resulting from poor glycemic control in early pregnancy) have proven harder to reduce, so terminations of pregnancy or neonatal death resulting from severe congenital anomalies now account for a large proportion of pregnancy losses in women with type 1 diabetes (6,8,9).

The developing epidemic of obesity over the last two decades has seen a substantial reduction in the age of onset of type 2 diabetes and its emergence in women of childbearing age. In many areas of the world, the number of pregnancies in women with type 2 diabetes now exceeds that of women with type 1 diabetes (6,10–13). A number of centers have reported higher rates of stillbirth or congenital anomalies in type 2 diabetic pregnancy, suggesting that the outcomes of pregnancy in type 2 diabetes can be worse than that for type 1 diabetes (6,14,15).

There are many reasons why pregnancy and neonatal losses might differ between type 1 and type 2 diabetes. Women with type 2 diabetes tend to be older, poorer, more obese, of higher parity, and to be from minority communities, all risk factors for poor pregnancy outcome, whereas women with type 1 diabetes are more likely to have vascular complications of diabetes. In this article, we report 20-year data from a single center on the rates and causes of pregnancy loss in women with type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Data were collected prospectively in diabetic women attending the Diabetes Pregnancy Service at the National Women's Hospital, whose pregnancies ended between 1 January 1986 and 31 December 2005. The service provides pregnancy care to diabetic women throughout the central, northern, and western areas of Auckland. The region has a large population of Polynesian origin, comprising the native Mâori and people from various Pacific Island nations and an increasing population of south and east Asian origin. Type 2 diabetes is common in these groups (16). This report incorporates data included in two previously published studies (6,17). Data collected included age, ethnic origin, parity, smoking status, height, and prepregnancy weight (from which BMI was calculated).

Classification of diabetes

Patients were classified as having type 1 diabetes if insulin had been used since diagnosis, or if there were serologic markers of islet autoimmunity. Patients were classified as having type 2 diabetes if they were not ketosis prone and did not require insulin for extended periods. Women with what we term "newly recognized " diabetes were diagnosed in pregnancy as having gestational diabetes, but on glucose tolerance testing 6 weeks postpartum still had diabetes, according to World Health Organization criteria. The majority of these women probably had

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Table 1—*Demographic features*

	All	Type 1 diabetes (known)	Type 2 diabetes (known)	Type 2 diabetes (new)	Type 1 diabetes (new)	Genetic causes
Number of pregnancies	1,200	330	540	314	11	5
Number of twin pregnancies	16	8	7	1	0	0
Age (years)	31.9 ± 5.5	29.2 ± 5.2	33.0 ± 5.1	32.9 ± 5.2	28.5 ± 6.3	35.4 ± 5.6
Prepregnancy BMI (kg/m^2)	31.1 ± 7.9	25.2 ± 4.5	33.9 ± 7.4	33.3 ± 7.9	23.2 ± 3.8	23.1 ± 5.1
Nulliparous (%)	29	50	18	24	46	40
Smoking in pregnancy (%)	15.3	13.6	20.2	8.6	4.3	0
Gestational age at presentation to service (weeks)	16.0 ± 9.7	9.7 ± 5.3	14.5 ± 7.9	25.3 ± 9.4	21.4 ± 7.8	12.0 ± 10.2
A1C at presentation (%)*	7.6 ± 1.6	7.6 ± 1.6	7.6 ± 1.7	7.1 ± 1.3	8.1 ± 3.3	6.7 ± 0.7
A1C at term (%)†	6.1 ± 0.9	6.1 ± 0.9	6.1 ± 0.9	6.4 ± 1.0	6.7 ± 1.3	5.6 ± 0.2
Number on insulin before pregnancy	395 (33)	329 (99.7)	57 (10.6)	0 (0)	0 (0)	1 (20)
Number not on insulin in pregnancy	61 (5.0)	0 (0)	17 (3.1)	43 (13.7)	1 (9.1)	0 (0)
Proportion with induction of labor or elective Cesarean section (%)	83.9	89.7	83.5	79.2	72.7	60.0
Gestational age at induction of labor or elective Cesarean section (weeks)	37.5 ± 2.7	37.2 ± 2.3	37.4 ± 3.1	37.9 ± 2.4	37.6 ± 1.8	35.0 ± 5.2
Cesarean section rate (%)	51.0	56.2	53.2	42.9	27.2	20.0
Ethnic group (%)						
European	35	91	16	6	64	100
Māori/Pacific	52	7	67	74	18	0
All others	13	2	17	20	18	0

Data are means ± SD or *n* (%) recorded in *583 pregnancies or †547 pregnancies.

undetected diabetes antedating their pregnancy. Data are included also from a small group of women with inherited forms of diabetes, proven by genetic testing. As these tests have become available only in recent years, it is probable that some women with genetic forms of diabetes have been classified as having type 2 diabetes.

Management of diabetes and pregnancy

All subjects undertook self-blood glucose monitoring. Insulin doses were adjusted to try to maintain fasting blood glucose in the range 4.0–5.5 mmol/l and 2-h postprandial levels <6.8 mmol/l. Glycemic control was assessed by A1C (nondiabetic values in the first trimester 4.6–5.6%). This assay was not accessible locally until 1997, so these data are available for only 583 pregnancies. Standard antenatal care included an ultrasound scan performed at 18–22 weeks' gestation to screen for fetal malformations. If detected before 24 weeks' gestation, women with fetuses with major malformation were offered termination of pregnancy. In otherwise uncomplicated pregnancies, labor was induced (or elective Cesarean section undertaken) between 37 and 40 weeks' gestation in women who had not delivered earlier. Neonatologists attended all deliveries.

Pregnancy losses

The time of pregnancy loss was recorded as either elective termination for medical reasons, intermediate fetal death (20–28 weeks' gestation), late fetal death (28 weeks' gestation to term), or early neonatal death (1 day to 1 month postpartum). Spontaneous miscarriages before 20 weeks' gestation and terminations for nonmedical reasons were not included, because complete ascertainment was not possible. The primary cause of pregnancy loss was assigned to one of five categories: major congenital anomalies, prematurity, chorioamnionitis, unexplained stillbirth (fetal death in utero), asphyxia during delivery, or other causes. Chorioamnionitis was diagnosed by the findings of inflammatory cells in the placenta and positive bacterial cultures of amniotic fluid.

Statistics

Proportions were compared using the χ^2 test and Fisher's exact test. Mean values were compared by Student's *t* test and ANOVA, with Tukey's post hoc test. Results are given as mean ± SD. Nonnormally distributed variables were compared by nonparametric tests. All analyses were performed using SAS version 9.1 (SAS Institute). CIs were calculated using the Confidence Interval Analysis Program version 2.1.1 (BMJ Publications).

RESULTS — In the 20-year period, there were 1,200 pregnancies in 903 women, including 16 twin pregnancies. In 325 women (27%), diabetes was unrecognized before pregnancy; of these, 314 (97%) had type 2 diabetes. Because they were usually identified by screening for gestational diabetes, women with newly recognized diabetes presented to our diabetes pregnancy service later in gestation than women with known diabetes ($P < 0.0005$). Women with known type 2 diabetes presented an average 5 weeks later in gestation than women with known type 1 diabetes ($P < 0.0001$) (Table 1).

The A1C at presentation was similar in women with known type 1 and type 2 diabetes. Women with newly recognized type 2 diabetes had a lower A1C at presentation than women with known type 2 diabetes ($P = 0.0047$). Women with newly recognized diabetes did not differ in age, BMI, or ethnic group distribution from women in the respective group of known diabetes. Women with type 2 diabetes had significantly greater BMI than women with type 1 diabetes ($P < 0.0001$) and were more commonly of non-European descent ($P < 0.0001$) (Table 1).

All women with type 1 diabetes and 97% of women with type 2 diabetes were treated with insulin during pregnancy,

Table 2—*Timing of pregnancy loss*

	Number of fetuses*	Elective termination <24 weeks	Intermediate fetal death	Late fetal death	Early neonatal death	Total losses
Type 1 diabetes (known)	338	5 (1.5)	1 (0.3)	0 (0)	3 (0.9)	9 (2.7)
Type 2 diabetes (known)	547	3 (0.5)	7 (1.3)	6 (1.1)	3 (0.5)	19 (3.4)
Type 1 diabetes (newly recognized)	11	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Type 2 diabetes (newly recognized)	315	0 (0)	4 (1.3)	5 (1.6)	4 (1.3)	13 (4.1)
Other diabetes	5	0 (0)	0 (0)	0 (0)	1 (20)	1 (20)
Total	1,216	8 (0.6)	12 (1.0)	11 (0.9)	11 (0.9)	42 (3.4)

Data are *n* (%). *Includes twin pregnancies.

but only 10.6% of women with known type 2 diabetes used insulin before pregnancy. Mean A1C values near term were similar in women with known type 1 and known type 2 diabetes. Women with newly recognized diabetes had higher mean A1C values near term than women with known diabetes ($P = 0.011$) (Table 1), reflecting their shorter duration of treatment.

There were a total of 42 pregnancy losses, 41 of which were in women with known type 1, known type 2, or newly recognized type 2 diabetes. The timing of the pregnancy loss according to type of diabetes is shown in Table 2. Comparing women with known or newly recognized type 1 diabetes with known or newly recognized type 2 diabetes, there was a significant difference in the distribution of pregnancy losses ($P = 0.006$), with intermediate and late fetal losses being uncommon in type 1 diabetes.

The causes of pregnancy loss are shown in Fig. 1. Twelve pregnancies were lost as a direct result of severe congenital anomalies; five were in women with type 1 and six in women with type 2 diabetes. In seven of these cases, the pregnancy was terminated after identification of severe malformations. In three cases (all in women with type 1 diabetes), the fetuses were affected by aneuploidy (trisomy 21 or trisomy 18). One baby born to a woman with mitochondrial diabetes died at the age of 10 days from a severe congenital cardiac anomaly. Four pregnancy losses were due to severe prematurity (the result of preterm labor at 23–30 weeks' gestation); in two cases, one of a twin pair was lost, and in two prematurity was the consequence of severe preeclampsia. Two babies born to women with newly recognized type 2 diabetes were born with severe hypoxia and died at 3 and 5 days of age, respectively. Five pregnancies were lost as a result of chorioamnionitis, all in women with known or newly recognized type 2 diabetes. There were 18 stillbirths, 17 of which were in women with known or newly recognized type 2 diabetes. The stillbirths clustered in two groups: eight occurring between 22 and 29 weeks' and 10 between 35 and 42 weeks' gestation (Fig. 1). The mean pregnancy BMI of women with stillbirths was 2 kg/m^2 greater than the mean of all women with type 2 diabetes ($P = 0.084$). The woman who had a stillbirth at 42 weeks' gestation had declined elective induction of labor. Comparing women with known or newly recognized type 1 diabetes with known or newly recognized type 2 diabetes, the cause of pregnancy loss differed significantly between the groups ($P = 0.017$). More than 75% of pregnancy losses in type 1 diabetes were due to congenital anomalies or prematurity, whereas in type 2 diabetes >75% of losses were due to stillbirth, chorioamnionitis, or birth asphyxia (Fig. 2). Stillbirth was significantly more prevalent in type 2 than in type 1 diabetes ($P = 0.028$).

To examine secular trends, we compared pregnancy losses across the two 10-year periods of the study (1986–1995 and 1996–2005). There were no substantial changes to diabetes management or fetal monitoring protocols over this time. In women with type 1 diabetes (both known and newly recognized), the rate of pregnancy loss was similar in the two periods (2.0% [95% CI 0.4–5.8] vs. 3.1% [1.2–6.7]). In women with type 2 diabetes (both known and newly recognized), it fell from 4.9% (3.0–7.5) to 2.8% (1.5–

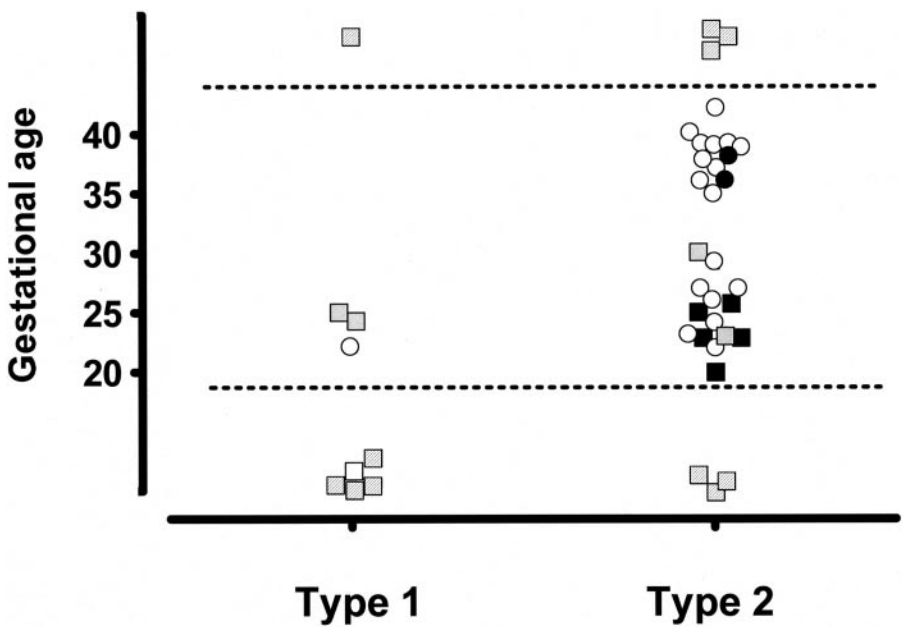

Figure 1—*Timing and cause of pregnancy loss in type 1 and type 2 diabetes (including newly recognized diabetes). Symbols beneath the lower dotted line represent terminations of pregnancy <24 weeks' gestation; symbols above the upper dotted line represent early neonatal deaths. Causes of pregnancy loss are indicated by the following symbols: ▨, congenital anomalies; ▤, prematurity; ■, chorioamnionitis; ○, unexplained stillbirth; ●, birth asphyxia; □, termination for severe hyperemesis.*

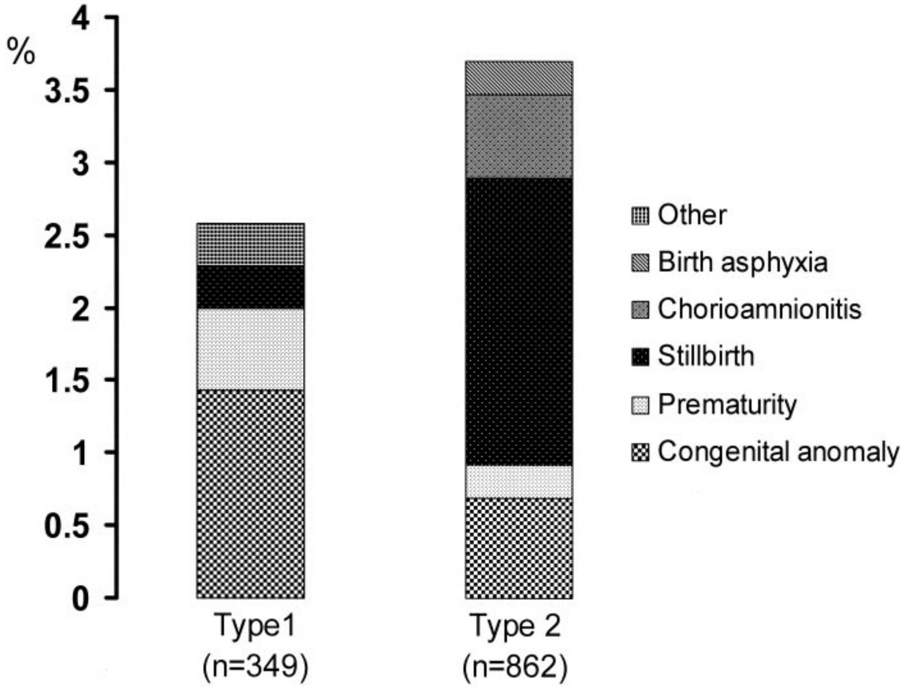

Figure 2—*Rates and causes of pregnancy loss in type 1 and type 2 diabetes (including newly recognized diabetes). The scale indicates percentage of the total number of fetuses.*

4.8), mainly because of a lower rate of late stillbirth (2.3% falling to 0.6%, P = 0.081). In the first decade, women with known type 2 diabetes presented to our service at a significantly later gestation than in the second decade (1986–1995: 16.5 ± 8.0 weeks vs. 1996–2005: 13.0 ± 7.5; $P < 0.0001$). The proportion of women with type 2 diabetes whose diabetes was not recognized before pregnancy decreased significantly in the second decade (1986–1995: 43% vs. 1996–2005: 32%; P = 0.0007). In the second decade, the age at presentation of women with known diabetes was just over a year greater than in the first decade ($P < 0.04$; both type 1 and type 2 diabetes), and the proportion of women who smoked in pregnancy decreased from 20% (1986–1995) to 15% (1996–2005) (P = 0.014). In women with known type 2 diabetes, the Cesarean section rate increased from 48% (in 1986–1995) to 58% (in 1996–2005) (P = 0.033), but Cesarean section rates were otherwise unchanged.

CONCLUSIONS— In this 20-year prospective study, we found that the rate of pregnancy loss was similar in type 1 and type 2 diabetes, but the causes of pregnancy loss differed significantly. In type 1 diabetes, the main causes were major congenital anomalies and neonatal complications of prematurity. The increased rate of major congenital anomalies in women with diabetes is related to glycemic control in early pregnancy (18,19). Although effective prepregnancy counseling reduces rates of congenital anomalies (20), it has proven hard to achieve nondiabetic rates (6,8,9). Three of 12 pregnancy losses attributable to congenital anomalies in our study were the result of fetal aneuploidy. The risk of aneuploidy is not related to glycemic control, and if these losses are excluded from the calculation, then the rate of pregnancy loss due to congenital anomalies was the same in type 1 and type 2 diabetes (0.6 vs. 0.7%). Over 20 years, mean maternal age increased in both type 1 and type 2 diabetes, reflecting changes in patterns of childbearing in the general population. In addition to an increased risk of aneuploidy, later pregnancy is associated with increased rates of twinning and stillbirth (21–23).

In type 2 diabetes, the major causes of pregnancy loss were stillbirth, birth asphyxia, and chorioamnionitis. Unexplained stillbirth and chorioamnionitis were strikingly more prevalent in women with type 2 diabetes than in women with type 1 diabetes. There were two clusters in unexplained stillbirths, and it is possible that some in the early cluster (20–29 weeks' gestation) were the result of unrecognized chorioamnionitis (Fig. 1). Stillbirth is associated with greater maternal age (22), but the difference in mean age between the women with type 1 and women with type 2 diabetes was only 3 years. Maternal obesity is strongly linked to pregnancy loss (23–25). For example, in the study of Kristensen et al. (25), the risk of stillbirth and neonatal death was doubled in women with a mean BMI >30 kg/m^2. The prepregnancy BMI exceeded this value in >70% of our subjects with type 2 diabetes. Maternal obesity, poverty, and hyperglycemia are all risk factors for chorioamnionitis (23,26,27). It is likely that obesity and low socioeconomic status (which cluster together) are major additional risk factors for pregnancy loss in our type 2 diabetes population.

Women with known type 2 diabetes typically present later to the Diabetes Pregnancy Service than women with known type 1 diabetes. This likely reflects the social disadvantage of many women with type 2 diabetes, lack of awareness (many had successful pregnancies before developing diabetes), and a lack of awareness of referring physicians. However, the glycemic control of women with type 2 diabetes was similar to that of women with type 1 diabetes, both at presentation and near term, so it is not clear what impact earlier referral in pregnancy might have. The temporal association between the earlier referral of women with type 2 diabetes and a lower rate of late stillbirth in the second decade of this study is encouraging, although one cannot infer causation.

We have argued that women with gestational diabetes who are shown to have diabetes on early postpartum testing should be considered as having newly recognized diabetes that likely antedated the pregnancy. Such pregnancies have the same risk of pregnancy loss and major congenital anomalies as established diabetes (6,17). Others (28) have also commented that the current definition of gestational diabetes is unhelpful as it groups together women with very differing degrees of glucose intolerance and, presumably, different degrees of risk. Most women with newly recognized diabetes have type 2 diabetes and share the same demographic and anthropometric features as women with known type 2 diabetes. In our population, for every three women with known type 2 diabetes we saw two with newly recognized type 2 diabetes. However, this ratio has changed, and in the second decade the proportion in whom type 2 diabetes was previously unrecognized was significantly smaller.

This probably reflects heightened awareness among physicians, midwives, and obstetricians of the significance of type 2 diabetes in women of childbearing age. A small proportion of the women with newly recognized diabetes (~1 in 30) proved to have type 1 diabetes. In our series, the presentation varied from modest hyperglycemia, not requiring insulin treatment, through to diabetic ketoacidosis. An increased rate of presentation of type 1 diabetes in pregnancy has previously been described (29).

Our report has some limitations. Being restricted to a single center, our findings are not necessarily applicable to other centers with different demography. Although our study is large, complete, and long term, we have not been able reliably to record spontaneous early pregnancy losses. Poorly controlled diabetes in early pregnancy is associated with an increased risk of spontaneous abortion (30). Because glycated hemoglobin measurements were not available before 1997, we are not able to compare glycemic control in the first decade with that in the second. Our return rate for postnatal glucose tolerance tests is ~70%, so it likely that some subjects with newly recognized–onset diabetes would be missed from our database.

Between-center variation in rates of pregnancy loss in diabetic women remains the subject of much debate (9). There are doubtless numerous factors that contribute to this variability, including the skill and experience of the team, the degree of integration between obstetric and diabetes services, and the demography of the population being served. Our data suggest that factors in addition to glycemic control have a substantial impact on both the rates and causes of pregnancy loss.

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