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

TIM CUNDY, MD1,2  GREG GAMBLE, MSc1  LEONIE NEALE, RM2
ROSE ELDER, FRACOG2  PAUL MCPHERSON, FRACOG2
PATRICK HENLEY, FRACP2  JANET ROWAN, FRACP2

1Department of Medicine, Faculty of Medical & Health Sciences, University of Auckland and 2Diabetes Pregnancy Service, National Women’s Health, Auckland City Hospital
Auckland, New Zealand

Running Title: Causes of pregnancy loss in type 1 and type 2 diabetes

Corresponding author:
Dr T Cundy Department of Medicine, Faculty of Medical & Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand
E-mail: t.cundy@auckland.ac.nz

Received for publication 20 March 2007 and accepted in revised form 15 June 2007.
Abstract

Objectives  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 type 1; 540 type 2) and 325 in women with diabetes diagnosed in pregnancy but persisting post-partum (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 prematurely; in type 2 diabetes >75% were attributable to stillbirth or chorioamnionitis (p= 0.017). Women with type 2 and type 1 diabetes had similar HbA1c 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.
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, hypoglycaemia and respiratory distress syndrome all took their toll [1]. Substantial improvement in the rates of perinatal mortality followed the development of centralised 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 non-diabetic 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 child-bearing 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 paper 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.

Patients and Methods

Data was collected prospectively in diabetic women attending the Diabetes Pregnancy service at 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 Māori 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 body mass index (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 six weeks post-partum still had diabetes, according to WHO criteria. The majority of these women probably had 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 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 post-prandial levels < 6.8 mmol/l. Glycemic control was assessed by glycated hemoglobin (HbA1c, 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 post-partum). Spontaneous miscarriages before 20 weeks' gestation and terminations for non-medical 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 X²-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 the mean (with standard deviation). Non-normally distributed variables were compared by non-parametric tests. All analyses were performed using SAS v9.1 (SAS Institute Inc). Confidence intervals were calculated using the Confidence Interval Analysis program v2.1.1 (BMJ Publications).

Results In the 20-year period there were 1200 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 HbA1c at presentation was similar in women with known type 1 and type 2 diabetes. Women with newly-recognized type 2 diabetes had a lower HbA1c 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, but only 10.6% of women with known type 2 diabetes used insulin before pregnancy. Mean HbA1c values near term were similar in women with known type 1 and known type 2 diabetes. Women with newly-recognized diabetes had higher mean HbA1c 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 Figure 1. Twelve pregnancies were lost as a direct result of severe congenital anomalies – 5 in women with type 1 and 6 in women with type 2 diabetes. In 7 of these cases the pregnancy was terminated after identification of severe malformations. In 3 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 aged 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 2 cases one of a twin pair was lost, and in 2 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 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 – 8 occurring between 22 and 29 weeks’, and 10 between 35 and 42 weeks’ gestation (Figure 1). The mean pregnancy BMI of women with stillbirths was 2kg/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 more than 75% of losses were due to stillbirth, chorioamnionitis or birth asphyxia (Figure 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 ten-year periods of the study: 1986-95 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 to 5.8) vs 3.1% (1.2 to 6.7). In women with type 2 diabetes (both known and newly-recognized) it fell from 4.9% (3.0 to 7.5) to 2.8% (1.5 to 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 (1986-95:16.5 [SD 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 (1986-95: 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% (1986-95) to 15% (1996-2005, p=0.014). In women with known type 2 diabetes the cesarean section rate increased from 48% (1986-95) to 58% (1996-2005, p=0.033), but cesarean section rates were otherwise unchanged.

Discussion

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 non-diabetic rates (6,8,9). Three of the 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 the twenty years mean maternal age increased in both type 1 and type 2 diabetes (0.6% vs 0.7%). Over the twenty 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 (Figure 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 >30kg/m². The prepregnancy BMI exceeded this value in more than 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 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 (28). 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 amongst 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 (about 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 paper 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 around 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 additional to glycemic control have a substantial impact on both the rates and causes of pregnancy loss.

Acknowledgements

We thank all the many staff who have given such excellent service over the past twenty years.
References


Table 1

Demographic features

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Type 1 known</th>
<th>Type 2 known</th>
<th>Type 2 new</th>
<th>Type 1 new</th>
<th>Genetic causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pregnancies</td>
<td>1200</td>
<td>330</td>
<td>540</td>
<td>314</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Number of twin pregnancies</td>
<td>16</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31.9 (5.5)</td>
<td>29.2 (5.2)</td>
<td>33.0 (5.1)</td>
<td>32.9 (5.2)</td>
<td>28.5 (6.3)</td>
<td>35.4 (5.6)</td>
</tr>
<tr>
<td>Prepregnancy BMI (kg/m²)</td>
<td>31.1 (7.9)</td>
<td>25.2 (4.5)</td>
<td>33.9 (7.4)</td>
<td>33.3 (7.9)</td>
<td>23.2 (3.8)</td>
<td>23.1 (5.1)</td>
</tr>
<tr>
<td>Nulliparous (%)</td>
<td>29</td>
<td>50</td>
<td>18</td>
<td>24</td>
<td>46</td>
<td>40</td>
</tr>
<tr>
<td>Smoking in pregnancy (%)</td>
<td>15.3</td>
<td>13.6</td>
<td>20.2</td>
<td>8.6</td>
<td>4.3</td>
<td>0</td>
</tr>
<tr>
<td>Gestational age at presentation to service (weeks)</td>
<td>16.0 (9.7)</td>
<td>9.7 (5.3)</td>
<td>14.5 (7.9)</td>
<td>25.3 (9.4)</td>
<td>21.4 (7.8)</td>
<td>12.0 (10.2)</td>
</tr>
<tr>
<td>HbA1c at presentation (%)*</td>
<td>7.6 (1.6)</td>
<td>7.6 (1.6)</td>
<td>7.6 (1.7)</td>
<td>7.1 (1.3)</td>
<td>8.1 (3.3)</td>
<td>6.7 (0.7)</td>
</tr>
<tr>
<td>HbA1c at term (%)**</td>
<td>6.1 (0.9)</td>
<td>6.1 (0.9)</td>
<td>6.1 (0.9)</td>
<td>6.4 (1.0)</td>
<td>6.7 (1.3)</td>
<td>5.6 (0.2)</td>
</tr>
<tr>
<td>Number on insulin before pregnancy</td>
<td>395 (33%)</td>
<td>337(99.7%)</td>
<td>57 (10.6%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Number not on insulin in pregnancy</td>
<td>61 (5.0%)</td>
<td>0 (0%)</td>
<td>17 (3.1%)</td>
<td>43 (13.7)</td>
<td>1 (9.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Proportion with induction of labor or elective cesarean section (%)</td>
<td>83.9</td>
<td>89.7</td>
<td>83.5</td>
<td>79.2</td>
<td>72.7</td>
<td>60.0</td>
</tr>
<tr>
<td>Gestational age at induction of labor or elective cesarean section</td>
<td>37.5 (2.7)</td>
<td>37.2 (2.3)</td>
<td>37.4 (3.1)</td>
<td>37.9 (2.4)</td>
<td>37.6 (1.8)</td>
<td>35.0 (5.2)</td>
</tr>
<tr>
<td>Cesarean section rate (%)</td>
<td>51.0</td>
<td>56.2</td>
<td>53.2</td>
<td>42.9</td>
<td>27.2</td>
<td>20.0</td>
</tr>
<tr>
<td>Ethnic group (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-European</td>
<td>35</td>
<td>91</td>
<td>16</td>
<td>6</td>
<td>64</td>
<td>100</td>
</tr>
<tr>
<td>-Māori/Pacific</td>
<td>52</td>
<td>7</td>
<td>67</td>
<td>74</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>-All others</td>
<td>13</td>
<td>2</td>
<td>17</td>
<td>20</td>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

Data given as mean (with SD), or as a number with percentage

* recorded in 583 pregnancies, ** recorded in 547 pregnancies
Table 2

Timing of pregnancy loss

<table>
<thead>
<tr>
<th></th>
<th>Number of fetuses*</th>
<th>Elective termination &lt;24 weeks</th>
<th>Intermediate fetal death</th>
<th>Late fetal death</th>
<th>Early neonatal death</th>
<th>Total losses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 – known</td>
<td>338</td>
<td>5 (1.5)</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
<td>3 (0.9)</td>
<td>9 (2.7)</td>
</tr>
<tr>
<td>Type 2 – known</td>
<td>547</td>
<td>3 (0.5)</td>
<td>7 (1.3)</td>
<td>6 (1.1)</td>
<td>3 (0.5)</td>
<td>19 (3.4)</td>
</tr>
<tr>
<td>Type 1 - newly recognized</td>
<td>11</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Type 2 - newly recognized</td>
<td>315</td>
<td>0 (0)</td>
<td>4 (1.3)</td>
<td>5 (1.6)</td>
<td>4 (1.3)</td>
<td>13 (4.1)</td>
</tr>
<tr>
<td>Other diabetes</td>
<td>5</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (20)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Total</td>
<td>1216</td>
<td>8 (0.6)</td>
<td>12 (1.0)</td>
<td>11 (0.9)</td>
<td>11 (0.9)</td>
<td>42 (3.4)</td>
</tr>
</tbody>
</table>

* includes twin pregnancies
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:
Dark grey squares – congenital anomalies; light grey squares – prematurity;
black squares – chorioamnionitis; open circles – unexplained stillbirth;
black circles – birth asphyxia; open square – 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.