Audit on Stillbirths in Women With Pregestational Type 1 Diabetes

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OBJECTIVE — To audit stillbirth cases in women with type 1 diabetes to search for specific characteristics in order to improve antenatal care and treatment

RESEARCH DESIGN AND METHODS — Retrospectively identified cases of stillbirths in women with type 1 diabetes during 1990–2000 were analyzed regarding characteristics of the mother, the pregnancy, glycemic control, and the stillborn. The cause of stillbirth was categorized as explainable, likely, or without obvious cause.

RESULTS — We found 22 women with 25 stillbirths among 1,361 singleton births by women with type 1 diabetes. In seven stillbirths the cause was categorized as explainable and in six as likely. In 12 cases no obvious cause was found; however, glycemic control was suboptimal in 9 of these cases. A total of 14 women reported daily smoking, and 10 of 19 with low education were unemployed.

CONCLUSIONS — Women experiencing stillbirth were characterized by a high incidence of suboptimal glycemic control, diabetic nephropathy, smoking, and low social status.

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Women with pregestational diabetes still have a five times increased risk of stillbirth compared with women with normal pregnancies (1). In the general population the risk of stillbirth in Denmark is 4.5 for every 1,000 deliveries (2), and stillbirths account for half of the cases of perinatal mortality, many of them being unexpected as well as unexplained (3–5). The literature on stillbirths by women with pregestational type 1 diabetes is very limited, and to our knowledge this is the only recent study focusing specifically on pregnancies ending in stillbirths in women with type 1 diabetes. The aim of the study was to audit stillbirth cases in women with type 1 diabetes to search for specific characteristics in order to improve antenatal care and treatment.

RESEARCH DESIGN AND METHODS

— The stillbirths were defined as intrauterine death after 24 weeks gestation and were identified retrospectively among 1,361 singleton births of women with pregestational type 1 diabetes. The women were followed during the period of 1990–2000 at three large tertiary centers in Denmark (Rigshospitalet Copenhagen, Aarhus University Hospital, and Odense University Hospital) that specialize in diabetes and pregnancy. These centers take care of approximately two-thirds of pregnant women with type 1 diabetes in Denmark.

Data were collected from the medical records with details on maternal age, White class (6), age at onset of diabetes, duration of diabetes, smoking habits, occupation, gestational age at the first visit to the center, gestational age at diagnosis of stillbirth, HbA_{1c} before pregnancy (within 2 months before conception), HbA_{1c} in early pregnancy (before 14 weeks of gestation) and in the last trimester (after 28 weeks' gestation), health during pregnancy, attendance to planned antepartum visits, nonstress testing, birth weight of the stillborn, and results from the autopsy report. Autopsy of the stillborn was routinely performed after permission from the mother and included microscopical analysis of placenta but not microbiological culture. Weekly antenatal testing with a nonstress test was routine in all three departments from approximately week 34. Information about the educational level and unemployment among the general Danish female population aged 20–40 years was obtained from the National Bureau of Statistics (Danmarks Statistik).

The causes of stillbirth were categorized as explainable (clear-cut explanation), likely, or without obvious explanation. Suboptimal glycemic control was defined as HbA_{1c} >7.5% (corresponding to 4 SD above mean) according to the recommendations from the American Diabetes Association (7). The reference range for HbA_{1c} in the background population of Copenhagen was 4.1–6.4% and was used as standard. The reference range from Aarhus and Odense was 4.4–6.4 and 5.4–7.4%, respectively. HbA_{1c} from these two centers was corrected to be able to compare HbA_{1c} values (see APPENDIX). HbA_{1c} was analyzed by antibody immunoassay (8) in the majority of pregnancies.

Gestational age (GA) was determined by early ultrasonography before 20 weeks' gestation in all cases except two, where the last menstrual period was used due to late enrollment. Birth weight in relation to GA and sex was calculated using

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Abbreviations: AGA, appropriate for gestational age; GA, gestational age; LGA, large for gestational age; SGA, small for gestational age.

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

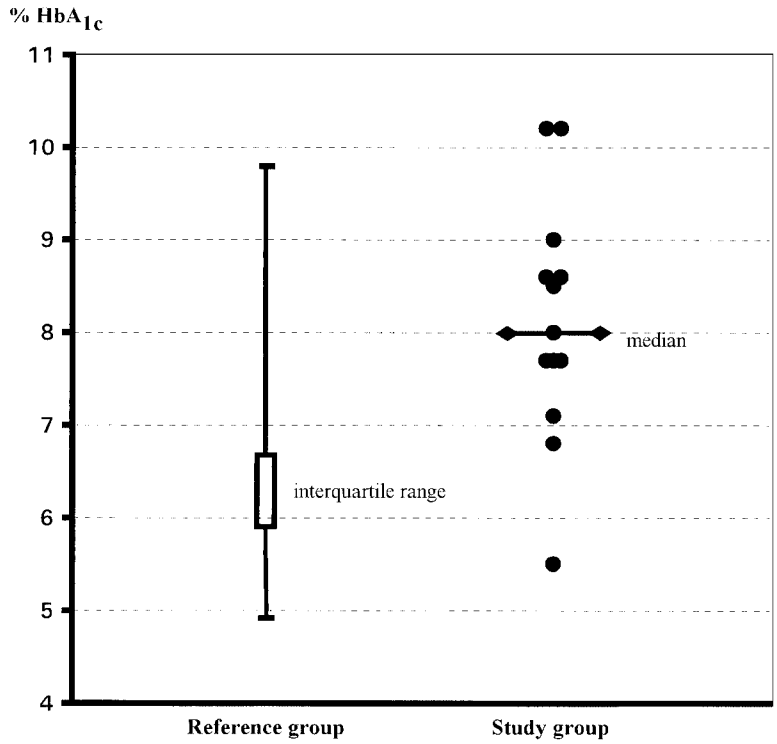

Figure 1—*Hemoglobin A_{1c} late in pregnancies resulting in stillbirths compared to reference group.*

a Danish linear growth curve (9). These curves are made for newborns with GA ≥28 weeks' gestation. In five cases with GA <28 weeks, birth weight was compared with data for normal fetal growth evaluated by longitudinal ultrasound examinations (10). Small for gestational age (SGA) was defined as birth weight below the 10th percentile, large for gestational age (LGA) as birth weight above the 90th percentile, and appropriate for gestational age (AGA) as birth weight between the 10th and 90th percentile. Birth weight in standard deviations from the mean in the background population was calculated (10).

The results are presented as medians and ranges. If a woman had more than one stillbirth in the study period, only the first stillbirth was included in the calculations of the medians, while all cases were included in the overall analysis.

The results were compared with a reference group of 236 consecutive pregnant type 1 diabetic women without stillbirths, followed at the center in Copenhagen in the years 1996–1999 (11). This group was chosen because it is well characterized, and no detailed data were available for the total population of pregnant women with type 1 diabetes in the three departments for the period 1990–2000. χ^2 test and Fisher's exact test were used as appropriate for comparisons of frequencies.

RESULTS — Of 22 women with type 1 diabetes, 25 stillbirths (1.8% of all singleton births by women with type 1 diabetes) were identified; 3 of the women had 2 stillbirths. Details for the individual stillbirths are presented in Table 1. An explainable cause was found in seven cases: chorioamnionitis, ketoacidosis, placental abruption, and severe intrauterine growth retardation. A likely cause was found in the six cases with autopsy records describing severe malformations in four cases, multiple placental infarctions in one, and thrombosis in the umbilical cord in one. In the remaining 12 cases of stillbirth no obvious explanation was found. However, in 9 of these 12 cases glycemic control in pregnancy was suboptimal. Overall, HbA_{1c} in pregnancy was considerably higher in women with stillbirths compared with the reference group (Fig. 1, Table 1) with 64% in stillbirth group versus 33% in reference group having suboptimal glycemic control early in pregnancy ($P = 0.004$). Late in pregnancy, suboptimal glycemic control was present in 67% in the stillbirth group and in 4% in the reference group ($P < 0.001$).

The incidence of major malformations was 10 times higher ($P < 0.001$) than in the reference group (Table 1), and all cases of stillbirths with malformation were found in the groups with explainable and likely causes. Of the 22 women, 6 (27%) suffered from diabetic nephropathy. The prevalence of diabetic nephropathy was only 5% in the reference group ($P < 0.001$). Preeclampsia was diagnosed in 18% of the women (case 6, 11, 19, and 20[a]) versus 12% in the reference group (not significant). Approximately half of the stillborns were large for gestational age; however, this was similar to the reference group.

In 20 cases the woman had been examined within the last week of the stillbirth. Among the five cases with examination beyond 1 week, three stillborns were severely macerated, indicating that the fetus had been dead for >3 days. In two of these cases the women reported fetal movements within 3 days (both stillborns AGA). The two women with diabetic ketoacidosis had not attended the hospital for >1 month before presenting with a stillbirth. In only seven cases a nonstress test was performed within 1 week from the diagnosis of stillbirth. Six tests were normal and one test in a growth-retarded fetus at 30 weeks' gestation was suspicious without indicating acute intervention. The six normal tests were all performed in the cases without an explainable cause of intrauterine death.

A total of 19 women had an occupation corresponding to no or only short education, and 10 of them were unemployed. The unemployment rate for the general Danish female population at age 20–40 years was 4.8–15.5%. There was no data available for reference group regarding social status. Daily smoking was reported by two-thirds of the women with stillbirth and by one-third in reference group ($P = 0.001$).

CONCLUSIONS — Suboptimal glycemic control before and in early pregnancy is known to be associated with high rates of congenital malformations and spontaneous abortions (12–14), and strict glycemic control before and throughout pregnancy seems to improve fetal outcome (15–17). In accordance

Table 1—*Characteristics for women with type 1 diabetes and stillbirth categorized according to possible cause of stillbirth*

Case[1]	Age (years)	White's class	Duration of diabetes (year)	Smoking	GA at first visit (week)	Pre-pregnancy HbA_{1c} (%)	Early HbA_{1c} (%)	Late HbA_{1c} (%)	GA (week)	Size at birth (SD)	Major malformations	Possible cause of stillbirth
1	27	C	10	Yes	9	—	7.3	7.7	30	SGA (−5.3)	No	Growth retardation
2	21	C	10	Yes	7	6.3	7.4	—	33	LGA (2.7)	No	Chorioamnionitis
4[a]	36	B	9	Yes	25	—	(6.2)[2]	—	34	LGA (2.4)	Microcephaly	Abruptio placentae
8	26	F	13	Yes	22	—	(7.9)[2]	—	26	AGA (−1.2)	No + cardiomyopathy	Ketoacidosis
9[a]	25	C	6	Yes	12	6.0	6.1	—	27	AGA (0.1)	—	Ketoacidosis
17	31	F	19	Yes	12	—	9.7	—	25	SGA (−5.7)	Facial	Growth retardation
20[a]	35	B	6	Yes	9	7.2	7.3	—	27	SGA (−4.6)	No	Growth retardation
4[b]	39	C	12	Yes	13	—	7.8	—	33	LGA (1.5)	Sacral dysgenesis + severe cardiomyopathy	Malformation
6	25	F	12	Yes	8	8.7	7.8	5.5	38	AGA (−0.6)	Cardiac[4] + severe cardiomyopathy	Malformation
7	19	C	9	Yes	11		8.1	—	28	LGA (2.5)	Cardiac[4]	Malformation
9[b]	28	C	8	Yes	11	6.8	7.6	6.0	36	LGA (2.3)	Cardiac[4]	Malformation
19	29	F	20	No	8	—	6.2	—	24	SGA (−4.7)	No	Multiple placental infarctions
21	27	B	1	—	11	—	9.2	8.6	37	LGA (3.2)	—	Umbilical cord
3	25	C	6	No	7	—	11.5	8.6	36	LGA (1.5)	No	Suboptimal glycemic control
5	24	F	13	No	26	—	—	7.7	35	AGA (1.2)	No	Suboptimal glycemic control
10	27	C	14	Yes	9	—	9.2	10.2	35	LGA (5.1)	No	Suboptimal glycemic control
11	27	B	2	—	5	7.9	7.8	7.1	36	AGA (0.9)	No	Suboptimal glycemic control
12	31	F	19	Yes	11	9.5	9.7	10.2	37	AGA (−0.3)	No	Suboptimal glycemic control
13	40	C	10	Yes	10	11.0	9.4	8.5	35	LGA (2.1)	—	Suboptimal glycemic control
15	28	D	23	No	5	8.8	8.6	9.0	35	LGA (3.6)	No	Suboptimal glycemic control
18	18	C	6	No	10	7.9	7.9	8.0	37	LGA (5.1)	No	Suboptimal glycemic control
22	34	D	22	Yes	13	9.0	8.3	7.7	37	LGA (1.6)	—	Suboptimal glycemic control
14	31	B	9	No	10	7.9	7.3	6.8	36	AGA (−0.2)	—	Unexplained
16	20	D	13	Yes	10	7.5	6.7	—	38	LGA (3.7)	No	Unexplained
20[b]	37	B	8	No	13	7.0	7.1	6.5	34	AGA (−1.0)	No	Unexplained
Stillbirth group												
Median[3]	27	[59% B+C]	11	[64%]	10	7.9	7.9	8.0	35	[52%]	[30%]	
(range)	(20–40)	[41% D+F]	(1–23)		(5–26)	(6.0–11.0)	(6.1–11.5)	(5.5–10.2)	(24–38)			
Reference group												
Median	30	[52% B+C]	14	[29%]	—	7.4 (n = 225)	7.0 (n = 219)	6.3 (n = 185)	37	[50%]	[3%]	
(range)	(19–43)	[48% D+F]	(½–35)			(5.0–11.6)	(4.4–9.9)	(4.9–9.8)				

Case number represents the chronological appearance of the stillbirth. Dotted lines separate the different groups of categorization of stillbirths (for details see text). [1]Cases with superscript *a* and *b*: first and second stillbirth for same mother. [2]The only HbA_{1c} measured in pregnancy was at first attendance in second trimester (not included in calculation of median). [3]Only first stillbirth included when calculating median. [4]Case 6, truncus arteriosus communis; case 7, aplasia of left ventricle and persistent left superior vena cava; case 9[b], coarctatio aorta and myocardial hypertrophy.

with this, the glycemic control did not improve during pregnancy in the stillbirth group in contrast to the reference group resulting in markedly higher HbA_{1c} values in late pregnancy. Furthermore the malformation rate was high. Overall suboptimal glycemic control during pregnancy was present in 67% of the pregnancies resulting in stillbirth. Suboptimal glycemic control during pregnancy ($HbA_{1c} > 7.5\%$) was the only "medical" finding in 36% of the stillbirths. This is in accordance with the study of Hanson et al. (18) who found a poor glycemic control as the only explanation in 5 of 10 cases of stillbirth in women with type 1 diabetes. Glycemic control in both early and late pregnancy was poorer in the stillbirth group when compared with reference group. In the stillbirth group HbA_{1c} did not decline during pregnancy as in the reference group. The difference in metabolic control between the stillbirth group and the control group were therefore greatest in late pregnancy around the time of stillbirth. Early as well as late suboptimal glycemic control may predispose to fetal distress, due to fetal hyperinsulinemia, acidosis, and hyperlacticemia, as maternal hyperglycemia and elevated HbA_{1c} are risk factors for fetal asphyxia, possibly leading to intrauterine death (19–21).

One-third of the women in the stillbirth group had diabetic nephropathy, which was six times higher than that in the reference group (11). In women with diabetic nephropathy, perinatal mortality is increased (22).

The proportion of unemployed women was four times higher in the stillbirth group than in the general Danish female population. Furthermore, the majority of the women in the stillbirth group were characterized by low educational level, and together with a high unemployment rate this expresses a low social status, which has also been associated with unexplained stillbirth and perinatal mortality (23,24). On the other hand, daily smoking, known to be related to social status, was reported by two-thirds of the women compared with less than one-third of the women in the reference group. In addition, smoking is a well-known risk factor for placental complications as found in four of the stillbirths (25,26).

Despite a routine with weekly nonstress testing from ~34 weeks' gestation, only 28% of our cases had a test performed within the last week before the diagnosis of stillbirth. This is partly explained by the fact that nine stillbirths occurred before 34 weeks' gestation. Nevertheless, a normal nonstress test cannot exclude an intrauterine death occurring within a few days after the test has been performed (27,28). The retrospective nature of the study design did not give the opportunity to decide whether some of the not-performed nonstress tests were due to flaws in the clinical setup or due to poor patient compliance. The lack of fetal surveillance together with the lacking improvement in glycemic control during pregnancy, the high rate of smokers, and the low social status indicate that this group has limited compliance, corresponding to the term "neglectors" introduced by Mølsted-Pedersen and Pedersen in 1967 (29).

In conclusion, our study identified the following characteristics of women with type 1 diabetes experiencing intrauterine death after 24 weeks' gestation: HbA_{1c} >4 SD above the range for the normal population, previous stillbirth, diabetic nephropathy, current smoking, and low social status. Our study indicates that more attention should be focused on these women during pregnancy, especially with respect to optimizing their glycemic control.

APPENDIX

Correction of HbA_{1c} was done by the following formula: (X − meanL)/1 SDL * 1 SDC + meanC, where X is the HbA_{1c} to be corrected, meanL is the mean from either Odense or Aarhus (6.4 and 5.4%, respectively), 1 SDL the SD from Odense or Aarhus (= 0.5 for both Odense and Aarhus), 1 SDC the SD from Copenhagen (= 0.575), and meanC the mean from Copenhagen (= 5.25). The corrections were done on the assumption that the values follow a normal distribution and that the reference range is the mean ± 2 SD.

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