Prepregnancy Care and Pregnancy Outcomes in Women With Type 1 Diabetes

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OBJECTIVE — The objective of this study was to examine the relationship between prepregnancy care, glycemic control, maternal hypoglycemia, and pregnancy outcomes in women with type 1 diabetes.

RESEARCH DESIGN AND METHODS — This was a prospective observational cohort study of women with type 1 diabetes who delivered from 1991 to 2002. Outcome measures were attendance at a clinic for prepregnancy care, maternal HbA_{1c} (A1C) throughout pregnancy, maternal severe hypoglycemic episodes, macrosomia, preeclampsia, premature delivery (delivery before 37 weeks), very premature delivery (delivery before 34 weeks), spontaneous abortion, and adverse pregnancy outcome (defined as major malformation, stillbirth, and neonatal death).

RESULTS — There were 290 pregnancies, in which 110 (38%) women had prepregnancy care. The prepregnancy care group contained more primiparous women (54.7 vs. 40.6%; $P = 0.021$) and fewer smokers (9.4 vs. 28.7%; $P < 0.0001$). They registered earlier (6.6 vs. 8.3 weeks, $P < 0.0001$) and had a lower A1C at the initial visit (6.5% vs. 7.6%; $P < 0.0001$). Adverse pregnancy outcomes and very premature deliveries were significantly lower in women who received prepregnancy care (2.9 vs. 10.2%; $P = 0.03$ and 5.0 vs. 14.2%; $P = 0.02$, respectively). In contrast, between groups, there was no difference in A1C after 24 weeks or in the rates of macrosomia, preeclampsia, or maternal severe hypoglycemic episodes.

CONCLUSIONS — Prepregnancy care was associated with improved glycemic control in early pregnancy and significant reductions in adverse pregnancy outcome (malformation, stillbirth, and neonatal death) and very premature delivery. However, prepregnancy care failed to have an impact on glycemic control in later pregnancy or to reduce the risk of macrosomia and preeclampsia.

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Diabetes is the most common medical condition to complicate pregnancy, affecting 1 pregnant woman in 250 in the U.K. (1). Women with type 1 diabetes have a poor outcome compared with women without diabetes, with increased rates of congenital malformations, preeclampsia, premature delivery, perinatal mortality, and risk of delivering a macrosomic baby (2). The Confidential Enquiry into Maternal and Child Health (CEMACH) confirms a nearly fourfold rise in perinatal mortality rates and twofold rise in congenital malformation rate in women with diabetes over baseline rates in England, Wales, and Northern Ireland (1). Studies suggest that the risk of adverse outcome (malformation and perinatal mortality) is related to poor glycemic control in early pregnancy (3,4). The critical time period for optimal glycemic control is before 7 weeks' gestation, during early organogenesis (5). Prepregnancy care is the only intervention that targets glycemic control at this critical early stage and has been associated with improvements in maternal and perinatal outcomes (4,6–13). The association of prepregnancy care with reduced risk of major congenital malformation has been further confirmed on meta-analysis (14). Some studies of macrosomia and preeclampsia suggest that these complications are related to glycemic control in early pregnancy and therefore may also be reduced by prepregnancy care (15–17).

However, many studies lack information on important confounding factors such as smoking status. Others have been criticized for lack of data on periconceptual use of folic acid (available for only one study in the meta-analysis), inadequate detail on glycemic control in later pregnancy, and poor descriptions of the type of antenatal care offered to women once pregnant (14). Much of the pregnancy outcome data on prepregnancy care dates back to the 1970s and 1980s, with only limited prospective data from studies carried out since 1990 (18,19).

It is well recognized that incidence of severe hypoglycemia is increased in pregnancy and is associated with tight glycemic control in early pregnancy (20). Indeed, it was originally observed that the offspring of women with increased numbers of hypoglycemic episodes had reduced rates of congenital malformation (21). One early study showed that prepregnancy care was associated with an increased risk of hypoglycemia (11), but the problem of hypoglycemia has not been addressed in recent studies of prepregnancy care.

The aim of our prospective study was to examine the relationship between attendance at a clinic for prepregnancy care, glycemic control throughout pregnancy, incidence of severe hypoglycemia, and pregnancy outcome including risk of macrosomia, preeclampsia, and premature delivery in women with type 1 diabetes.

RESEARCH DESIGN AND METHODS

— This was a prospective observational cohort study including all pregnant women with type 1 diabetes who received their antenatal care and delivered in Norwich, U.K., between 1991 and 2002. The hospital serves a resident population of 510,000 of predominantly Caucasian ethnicity. Women were excluded if they received only part of their antenatal care in Norwich and terminated

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

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their pregnancy for nontherapeutic reasons. Ethical approval was obtained from the Norfolk and Norwich University Hospital Ethics Committee, and informed consent was obtained from all participants.

Prepregnancy and antenatal care

A formal preconception service was established in 1990 and was staffed by a consultant physician and a senior diabetes specialist nurse. All women with type 1 diabetes are reviewed regularly in the hospital diabetes center. Women of childbearing age are asked about plans for pregnancy during routine clinic visits and are encouraged to attend the center for prepregnancy care if they plan to become pregnant in the near future.

Women attending the center for prepregnancy care were seen every 1–3 months by the consultant physician and also the diabetes specialist nurse. All were reviewed by a dietitian. Women were advised to monitor capillary blood glucose four to seven times daily and aim for preprandial blood glucose <6 mmol/l, postprandial blood glucose <8 mmol/l, and a target HbA_{1c} (A1C) <7.5% before conception. Women were educated about the increased risk of severe hypoglycemia during pregnancy, loss of hypoglycemic awareness during pregnancy, and risk of increased insulin sensitivity in early pregnancy and late pregnancy and instructed on the use of glucagon.

All women were advised to take folic acid supplementation before or as soon as they discontinued contraception and to avoid the use of certain drugs, e.g., ACE inhibitors and/or statins, with smoking cessation advice given as required. All women in this study attend hospital clinics; they are advised to contact the diabetes team by telephone if they become pregnant and would be registered into the diabetes antenatal clinic in the following week. All women received the same antenatal care, which involved fortnightly (occasionally weekly) visits to the diabetes antenatal clinic. Women were managed with short-acting insulin before meals with intermediate-acting insulin once or twice daily. Insulin analogs were not being used for diabetes in pregnancy during the study period.

Data collection and outcome measures

All women were screened for complications of diabetes, and those with a history of treated retinopathy or any degree of nephropathy were defined as having microvascular complications. Smoking status was documented as positive if the woman smoked at the time of her first visit to the diabetes antenatal clinic. Severe hypoglycemic episodes were defined as any episode of hypoglycemia needing external assistance for recovery, and all episodes of severe hypoglycemia were recorded at each clinic visit. A1C was measured every 4 weeks and assayed using the Biomen 8140 method (normal range 3.6–5.8%).

Adverse pregnancy outcome measures were major congenital malformation (defined as potentially life-threatening or associated with major long-term disability; spontaneous abortion was excluded), stillbirth (defined as death after 22 weeks' gestation), and neonatal death (death within 28 days after delivery). Pregnancy complications included severe hypoglycemia, spontaneous abortion (<22 weeks), macrosomia, preeclampsia, premature delivery (before 37 weeks), very premature delivery (before 34 weeks), and cesarean section. Macrosomia was defined as birth weight >90th centile, matched for gestational age and sex. Preeclampsia was defined as blood pressure >140/90 mmHg on two occasions with protein excretion >300 mg in 24 h.

Statistical analyses

Univariate comparisons between patients receiving and not receiving prepregnancy care were performed using Pearson's χ^2 test for categorical variables and Student's *t* tests for continuous variables. For multivariate comparisons, logistic regression analysis was performed with backward elimination using a *P* value of >0.10 as the threshold for removing a variable. The response variables of interest were spontaneous abortion, adverse pregnancy outcome (malformation, stillbirth, and neonatal death), macrosomia, preeclampsia, premature delivery, and cesarean section. Predictor variables entered into the model were diabetes duration, prepregnancy care, maternal age, parity, cigarette smoking at conception, maternal weight, A1C at registration and at 12 and 24 weeks' gestation, and the presence of microvascular complications. Statistical analyses were performed using S-plus 6.2 (Insightful).

RESULTS — We present the results of 290 pregnancies in women with type 1 diabetes during the study period. Two women declined to participate in the study. Two women (1%) were non-Caucasian. No women were receiving statins before conception, and only one woman was receiving an ACE inhibitor before conception.

There were 28 (9.7%) spontaneous abortions, 13 (4.5%) congenital malformations, 5 stillbirths, and 2 neonatal deaths (perinatal mortality rate of 27 of 1,000 births). Eight women had medical pregnancy terminations for congenital malformations, and one woman had a medical termination for Patau's syndrome (trisomy of chromosome 13). There were six neural tube, three cardiac, two skeletal, and two urogenital malformations. Both neonatal deaths were related to delivery before 26 weeks. Two stillbirths occurred before 28 weeks, and three stillbirths occurred between 37 and 38 weeks' gestation.

A total of 110 (38%) women attended the center for prepregnancy care. Comparing 1997–2002 with 1991–1996, we found a significant increase in the proportion of women accessing prepregnancy care (44.8 vs. 31.6%, $P = 0.023$). Between women who did or did not receive prepregnancy care, there was no significant difference in mean maternal age (29.4 vs. 28.6 years), mean duration of diabetes (12.9 vs. 13.6 years), mean maternal weight (69.8 vs. 68.6 kg), or the presence of microvascular complications (8.7 vs. 8.1%) (Table 1). There were significantly more primiparous women (54.7 vs. 40.6%, $P = 0.02$) and significantly fewer smokers (9.4 vs. 28.7%, $P < 0.0001$) in women who did receive prepregnancy care. Women accessing prepregnancy care signed up in the diabetes antenatal clinic significantly earlier than women who did not (mean 6.6 vs. 8.3 weeks, $P < 0.0001$). Women who had not received prepregnancy care were rarely receiving folic acid supplements before they attended the antenatal clinic.

At the initial visit, 82.7% of women with prepregnancy care had an A1C ≤7.5% and 62.7% had an A1C <7% compared with 50% of women without prepregnancy care with an A1C ≤7.5% and 35.4% with A1C <7% ($P < 0.0001$ and $P < 0.0001$, respectively). In those women with no prepregnancy care, 53.3% of multiparous women had an A1C ≤7.5% compared with 46.6% of primiparous women. A1C was significantly lower in women who received prepregnancy care at registration (mean 6.5 vs. 7.6%, $P < 0.0001$) and remained lower

Table 1—*Characteristics of women with type 1 diabetes who did or did not receive prepregnancy care*

	Prepregnancy care	No prepregnancy care	*P* value
n	110	180	
Maternal age (years)	29.4 ± 4.3	28.6 ± 5.4	NS
Diabetes duration (years)	12.9 ± 8.3	13.6 ± 8.1	NS
Maternal weight (kg)	69.8 ± 11.4	68.6 ± 10.5	NS
Diabetes complications (%)	8.7	8.1	NS
Primiparous women (%)	54.7	40.6	0.02
Smokers (%)	9.4	28.7	<0.0001
Booking gestation (weeks)	6.6 ± 1.8	8.3 ± 2.6	<0.0001
Pregnancy complications*			
Delivery <34 weeks (%)	5.0	14.2	0.02
Delivery <37 weeks (%)	25.0	33.6	NS
Macrosomia (%)	44.0	43.4	NS
Preeclampsia (%)	13.1	12.7	NS
Cesarean section (%)	66.3	65.5	NS
Pregnancy outcome†			
Spontaneous abortion	6 (5.7)	22 (14.0)	0.056
Malformation	2	11	0.065
Stillbirth	1	4	NS
Neonatal death	0	2	NS
Adverse outcome‡	3 (2.9)	16 (10.2)	0.026

Data are means ± SD unless otherwise indicated. *Pregnancy complications are expressed as % live births. †Pregnancy outcomes are given as number (%) with percentages expressed as % of total number of pregnancies. ‡Adverse outcomes include congenital malformations, stillbirths, and neonatal deaths.

throughout early pregnancy (Table 2). However, the difference in glycemic control became less marked with increasing gestation with no significant differences from 28 weeks onward. There was no significant difference in the incidence of severe hypoglycemia between women who did or did not receive prepregnancy care (42.5 vs. 36.2%, $P = 0.30$).

There were significantly fewer adverse pregnancy outcomes (malformations, stillbirths, and neonatal deaths) in women with prepregnancy care compared with women without prepregnancy care (2.9 vs. 10.2%, $P = 0.03$). In addition, there appeared to be a reduction in spontaneous abortions (5.7 vs. 14.0%, $P = 0.056$). There were also significantly fewer very premature deliveries (delivery before 34 weeks) in women with prepregnancy care (5.0 vs. 14.2%, $P = 0.02$) (Table 1). In contrast, between women with and without prepregnancy care, there was no significant difference in rates of delivery before 37 weeks, preeclampsia, macrosomia, or cesarean section.

The benefit of prepregnancy care was not explained by differences in confounding factors between the two groups. Multivariate logistic regression analysis showed that not having received prepregnancy care (odds ratio [OR] 3.89 [95% CI 1.35–11.18]; $P = 0.006$), primiparity (2.74 [1.10–6.81]; $P = 0.03$), and duration of diabetes (1.32 [1.00–1.75]; $P = 0.05$) were all independently associated with very premature delivery (Table 3). Variables not independently associated with very premature delivery were maternal age and weight, smoking at conception, A1C at registration and 12 and 24 weeks' gestation, and microvascular complications. Variables independently associated with spontaneous abortion, congenital malformation, stillbirth, and perinatal death were lack of prepregnancy care (5.9 [1.7–20.4]; $P < 0.0009$), the presence of microvascular complications (5.9 [1.0–35.2]; $P < 0.05$), duration of diabetes (1.3 [1.0–1.6]; $P < 0.07$), and A1C at the initial visit (1.3 [1.0–1.6]; $P < 0.03$). Variables not associated with spontaneous abortion and adverse pregnancy outcome were maternal age and weight, smoking at conception, and A1C at 12 and 24 weeks' gestation.

Table 2—*Glycemic control during pregnancy in women who did or did not receive prepregnancy care*

A1C*	Prepregnancy care	No prepregnancy care	*P* value
Booking	6.5 ± 1.1	7.6 ± 1.7	<0.0001
12 weeks	5.9 ± 0.9	6.6 ± 1.2	<0.0001
16 weeks	5.7 ± 0.9	6.1 ± 1.2	0.002
20 weeks	5.5 ± 0.9	5.8 ± 1.0	0.01
24 weeks	5.5 ± 0.9	5.7 ± 1.0	0.045
28 weeks	5.5 ± 0.8	5.8 ± 1.0	NS
32 weeks	5.6 ± 0.8	5.8 ± 1.0	NS

Data are means ± SD. *A1C assay normal reference range 3.6–5.8%.

CONCLUSIONS — This is the most comprehensive cohort study of prepregnancy care in women with type 1 diabetes in the U.K., describing glycemic control throughout pregnancy and multiple pregnancy outcomes. In addition, we have complete follow-up on a large and recent unselected clinic population, a collection of monthly A1C measurements from a single laboratory, and careful assessment of potential confounding factors. The prepregnancy clinic was attended by 38% of women, which is in keeping with findings from the CEMACH report (1). There was a significant increase in numbers of women receiving prepregnancy care during the study. This figure is lower than that of 58% reported in a recent study from Denmark (22). In that study, preconception guidance was not defined, and only 34% women were monitoring their blood glucose at the time of conception compared with 100% women in our study. This might suggest that the preconception guidance had been limited compared with prepregnancy care in our study.

Our study shows that, in women with type 1 diabetes, receiving prepregnancy care is associated with improved glycemic control in early pregnancy. Although the improvement in glycemic control was most significant in the first 20 weeks of pregnancy, it was not associated with the increased risk of severe hypoglycemia seen in earlier studies (11,23). We suggest that this result is due to increased awareness about the risk of hypoglycemia in pregnancy by the health professionals and also education of the women with diabetes, as has been shown by Howorka et al.

Table 3—*Independent predictors of very premature delivery (<34 weeks) and spontaneous abortion, congenital malformation, stillbirth, and perinatal death in women with type 1 diabetes*

Outcome variable	Adjusted OR (95% CI)	*P* value
Very premature delivery		
No prepregnancy care	3.89 (1.35–11.18	0.006
Parity*	2.74 (1.10–6.81)	0.03
Diabetes duration†	1.32 (1.00–1.75)	0.05
Spontaneous abortion, malformation, stillbirth, neonatal death		
No prepregnancy care	5.9 (1.7–20.4)	0.0009
Microvascular complications	5.9 (1.0–35.2)	0.05
A1C at registration‡	1.3 (1.0–1.6)	0.03
Duration of diabetes†	1.3 (1.0–1.6)	0.07

*Risk associated with primiparity compared to multiparity. †OR refers to proportional increase in odds for every extra 5 years duration of diabetes. ‡OR refers to proportional increase in odds with each 1% increase in A1C.

(24) in their study of functional insulin treatment programs in pregnancy. Prepregnancy care resulted in subsequently reduced risk of spontaneous abortion, adverse pregnancy outcome (major congenital malformation, stillbirth, and perinatal death), and very premature delivery. Our data show a highly statistically significant association between prepregnancy care and very premature delivery and suggest that not having received prepregnancy care was an important predictor of very premature delivery, even after correction for potential confounding factors including smoking status. A recent French study of premature delivery in women with type 1 diabetes suggested that the risk of premature delivery was related to glycemic control around the time of delivery (25). In contrast, our results suggest that early glycemic control is also important as the benefits of prepregnancy care on glycemic control were greatest in early pregnancy. Although we did not document neonatal admissions, we suggest that this reduction in deliveries before 34 weeks would have had a very positive impact.

The benefits of prepregnancy care were not explained by certain possible confounding factors such as smoking, maternal age, and maternal weight. In addition to emphasis on tight glycemic control and early registration, prepregnancy care included prescribing of folic acid supplements for all women whereas patients with no prepregnancy care were rarely taking folic acid supplements at conception. No patients were receiving statins at conception, and only one patient was receiving an ACE inhibitor at conception. All women in the study had received diabetes care from a hospital diabetologist before pregnancy and <1% was of non-Caucasian ethnicity. Data were not collected on the qualitative measure of planning of the pregnancy, but we concur with views expressed previously by both Steel et al. (11) and Holing et al. (26) that many women in the non–prepregnancy care group were pleased to be pregnant and had often either not been using contraception or using it unreliably. Data on socioeconomic status and level of maternal education were not collected, and these may have been factors in whether patients requested prepregnancy care as has been suggested by Holing et al. (26).

An association between accessing prepregnancy care and a reduced risk of spontaneous abortion was suggested in an earlier study (10). Despite the inherent difficulties in trying to capture all spontaneous abortions, it is important to reexamine this relationship because the risk of spontaneous abortion is increased in women with poorly controlled type 1 diabetes (27). We found a trend ($P = 0.056$) toward a reduction in spontaneous abortions in women receiving prepregnancy care compared with those who did not. Moreover, the magnitude of reduction in rates of spontaneous abortion may be underestimated because women not receiving prepregnancy care registered significantly later for antenatal care, with the possibility that some spontaneous abortions in this group may have been missed.

We found no differences in the risk of preeclampsia or macrosomia in women who did receive prepregnancy care compared with women who did not, despite evidence that these complications are related to poor glycemic control (15,17,28–30). One possible explanation for our findings is that the risk of preeclampsia and macrosomia is related to glycemic control in later rather than early pregnancy because we found the benefits of prepregnancy care on glycemic control were restricted to the first 24 weeks of gestation. Our rates of macrosomia and preeclampsia are strikingly similar to those in a recent prospective study in the Netherlands of 42.6 and 12.8%, respectively, compared with the Dutch rates of 45.1 and 12.7% (2). Currently, despite their relationship with glycemic control, we appear not to have effective tools to optimize glycemia and reduce these risks.

Several studies have analyzed characteristics of women receiving prepregnancy care and have shown that these women are more likely to be married or in stable relationships, have higher incomes, and are better educated than women not receiving prepregnancy care (18,31). It had therefore been suggested by some authors that women attending clinics for prepregnancy care are a self-selected group who are more able to achieve good glycemic control (31). However, our results show that there was no significant difference in glycemic control between the groups in the second half of pregnancy, suggesting that the women who had not accessed prepregnancy care are capable of achieving the same level of glycemia as women receiving prepregnancy care even if they are of a different socioeconomic status or educational background.

Our study is novel in documenting the duration of benefit associated with prepregnancy care on glycemic control. Because A1C reflects glycemic control over the preceding 6–8 weeks, our data showing significant differences in A1C between groups from registration until 24 weeks' gestation suggest that improved glycemic control in the prepregnancy group continues until 16–18 weeks' gestation. The rapid reduction in A1C values between the initial visit and 12 weeks' gestation in both groups emphasizes the importance of early first trimester assessment and demonstrates that glycemic assessment at the end of the first trimester does not adequately represent glycemic control at the time of organogenesis.

During this study, great emphasis was placed on glucose monitoring in the prepregnancy care, and the aim was for an A1C <7.5% before conception. Recent

guidelines suggest that when planning a pregnancy, women with type 1 diabetes should aim for the lowest A1C possible without undue risk of hypoglycemia, and the authors support these recommendations. However, during the study period, no women were using insulin pumps or analog insulins. Despite intensive input and support in the prepregnancy group, 13% of women were unable to achieve an A1C <7.5 and 37% of women were unable to achieve an A1C <7% at registration. Hopefully, newer technologies such as insulin pumps and glucose monitoring systems along with analog insulins will enable women to achieve better glycemic control both at initial registration and in later pregnancy.

In summary, the results of our study show that accessing of prepregnancy care is associated with earlier antenatal registration, improved glycemic control in the first half of pregnancy, and a reduced risk of spontaneous abortion, adverse outcome (malformation or perinatal death), and delivery before 34 weeks' gestation. It is therefore essential that researchers and clinicians refocus on prepregnancy care to improve the use of these services, to examine the views of nonparticipants and determine how we can engage those most at risk of poor outcomes, and to evaluate the role of prepregnancy care for the growing numbers of women with type 2 diabetes, for whom existing services are failing (1). We also need to address the fact that, however effective prepregancy care is in early pregnancy, it fails to reduce the risks of macrosomia and preeclampsia. We believe that further study is required to optimize glycemic control in later pregnancy and that perhaps, by combining prepregnancy care with additional education during pregnancy and/or exploring the use of new technologies and analog insulins, glycemic control could be optimized throughout pregnancy.

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