Spontaneous abortion and diabetes mellitus

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Summary

In 58 consecutive pregnancies in insulin-dependent diabetic women, glycosylated haemoglobin levels were abnormally high in 78% at the time of booking for antenatal care.

Spontaneous abortion was the outcome in 15 pregnancies, 10 occurring before the 15th week of gestation. Glycosylated haemoglobin levels were significantly higher in those women who aborted spontaneously than in women who delivered successfully ($12.8 \pm 1.8\%$ v. $11.2 \pm 2.3\%$, mean $\pm$ s.d.). These results emphasise the inadequacy of diabetic control in the first trimester and lend further support to the importance of good control at this critical time in insulin-dependent diabetes.

KEY WORDS: spontaneous abortion, diabetes mellitus.

Introduction

Studies of diabetic control during the first critical weeks of pregnancy are difficult unless accurate monitoring of blood glucose has already started before booking for antenatal care. With the introduction of the measurement of glycosylated haemoglobin (HbA₁) which reflects overall blood glucose control over the previous 2 months, it is now possible to study the effect of this particular aspect of metabolic control on the early stages of pregnancy. Previous studies have shown that elevated HbA₁ concentrations are found in pregnant diabetics at presentation (Leslie *et al.*, 1978) and are associated with a greater prevalence of major congenital anomalies in the infants (Miller *et al.*, 1981). Spontaneous abortions were once considered to be common in insulin-dependent diabetes (Pedersen, 1967), but more recent series of pregnancies complicated by

diabetes have not confirmed these impressions (Drury, Greene and Stronge, 1977; Kitzmiller, Clougherty and Younger, 1978).

We have measured HbA₁ concentrations in 58 consecutive pregnancies in insulin-dependent diabetic mothers in an attempt to detect a relationship between metabolic control and outcome of pregnancy and to assess the adequacy of diabetic treatment at the time of booking.

Patients and methods

Fifty-eight consecutive confirmed pregnancies in 52 Caucasian patients with insulin-dependent diabetes were managed at a joint antenatal diabetic clinic. Sixteen patients were in White's class B (Hare and White, 1980), 21 class C, 12 class D and 3 class R, including one patient with mild renal impairment. Clinical details about illness, drugs taken and smoking habits were obtained at the first visit and also from an additional questionnaire completed by the patient between the first and second clinic visit. In 55 pregnancies, the first visit was before 14 weeks gestation and in the remaining three between 14 and 18 weeks gestation.

Spontaneous abortion or delivery occurred between February 1979 and June 1981 inclusive. The products of conception were examined histologically and spontaneous abortions subdivided into early (9-14 weeks) when associated with a blighted ovum or early embryonic death, and late (16-25 weeks) abortions with normal fetus. Major congenital abnormalities were sought in all infants delivered at 28 or more weeks gestation.

At booking, capillary blood glucose was measured by an automated glucose oxidase method on blood taken between 09.30 and 10.30 hr before the mid-

morning snack, and at subsequent fortnightly clinic visits. Glycosylated haemoglobin (HbA₁) was measured on venous blood taken into EDTA. HbA₁ was measured by a microcolumn method (Kynock and Lehmann, 1977) with the exception that buffer no. 2 was 20% stronger and all assays were performed at room temperature (between 16–21°C).

The intra-assay coefficient of variation was 3.3%. HbA₁ was measured in 208 non-pregnant normal female subjects with normal fasting blood glucose levels.

Results

The mean percentage HbA₁ in all women at the first clinic visit was 11.5 ± 2.2 s.d. (range 6.1–16.9%) which was significantly greater than the non-pregnant subjects (8.0 ± 0.89 s.d., range 6–10%, $P < 0.001$, unpaired *t*-test). In 45 patients (78%), the HbA₁ level was above the upper limit of the range found in normal subjects.

Fifteen spontaneous abortions occurred (28%); 7 were blighted ova, 3 were early embryonic deaths and 5 were late abortions. The medical and obstetric data of the patients who aborted did not differ significantly from those who delivered at or after 28 weeks gestation (Table 1). Of the late abortions, one occurred at 21 weeks gestation in a twin pregnancy and one in a patient in whom a Shirodkar suture had been inserted because of previous abortions and premature delivery. The remaining patients who aborted did so unexpectedly and no external malformations were noted in the fetuses from the late abortions.

HbA₁ was elevated in the first trimester in the 10 pregnancies which ended in early spontaneous abortion ($12.8 \pm 1.8\%$; mean $\pm$ s.d.) compared with those that delivered at 28 or more weeks gestation ($11.2 \pm 2.3\%$, $P < 0.05$, unpaired *t*-test). In the late abortion group, HbA₁ was not different from those that delivered at 28 or more weeks gestation. HbA₁ was less than 11% in only 3 of the 15 patients who aborted compared with 24 of the 43 patients who delivered at 28 or more weeks gestation [χ^2 with Yate's correction = 4.3837, $P < 0.05$ (Fig. 1)]. In the 5 patients who had both a spontaneous abortion and a normal delivery during the course of the study, the HbA₁ level was higher, but not significantly so, at the corresponding gestational age in 4 pregnancies that aborted ($12.4 \pm 1.8\%$ v. $10.8 \pm 2.3\%$).

HbA₁ level did not correlate with the blood glucose taken at the same time ($r = 0.16$) and the blood glucose levels at the first visit to the clinic were not significantly higher in those that aborted (mean 8.6 mmol/l ± 2.8 s.d.) compared with those that delivered at 28 or more weeks gestation (mean 8.4 mmol/l ± 4.4 s.d.).

FIG. 1. Glycosylated haemoglobin levels (% HbA₁) when first seen at the antenatal clinic. The open circles indicate levels in 2 pregnancies delivered of infants with major congenital abnormalities. The dotted line indicates the extreme upper limit of the range found in normal women.

Discussion

The wide range of HbA₁ levels in the first trimester of pregnancy complicated by diabetes, has been reported by others (Leslie *et al.*, 1978; Miller *et al.*, 1981). The initial HbA₁ level was not significantly related to the severity of diabetes, classified on clinical criteria, though we noted a trend towards higher levels with increasing White's class as reported by O'Shaughnessy, Russ and Zuspan (1979).

It is unlikely that the apparent HbA₁ levels were elevated by other haemoglobins, particularly haemoglobin F. Though transplacental haemorrhage may occur in association with abortions of all types, in most abortions less than 0.1 ml fetal red cells have been transferred and only rarely greater than 1 ml (WHO, 1971). We do not know the extent to which the HbA₁ level included an increase occurring *in vitro*, particularly in those samples with a raised blood glucose. All samples were handled in a similar manner and there was no significant correlation

TABLE 1. Comparison of diabetic women with spontaneous abortions and normal deliveries.

	Spontaneous abortion	Delivered at or after 28 weeks gestation
<i>n</i>	15	43
Mean age (years) (range)	26(19-35)	27(18-37)
Mean duration of diabetes (years) ($\pm$ s.d.)	11.8 $\pm$ 9.1	10.8 $\pm$ 6.6
White's Class		
B	2	15
C	9	16
D + R	4	12
% smokers	53	44
% patients ill before first visit*	20	30
Patients on drugs before first visit:		
iron	2	7
folic acid	1	2
other vitamins	—	3
dicyclomine	—	3
promethazine	—	2
antibiotics	2	3
analgesics	1	5
clomiphene	1	1
other	1	7
no drugs	9	24
Primigravida	6	14
Twins	1	—
Previous termination of pregnancy	5	5
Previous spontaneous abortion	4	9

*Mainly upper respiratory tract infections.

between HbA₁ and the corresponding blood glucose level. Blood glucose levels in those that aborted were not significantly different from those that delivered at 28 or more weeks gestation.

It is generally considered that abortions in insulin-dependent diabetic women occur as in the non-diabetic population. Collected series between 1954 and 1961 averaged 10% spontaneous abortions (Kyle, 1963) and more recent reports have shown similar rates between 8.7% and 12% (Drury *et al.*, 1977; Kitzmiller *et al.*, 1978). There are no reliable statistics for abortion in the population as a whole due to variations in the reporting of abortions and clinic booking practices, but it is commonly held that about 15% of all pregnancies abort. It is likely that the prevalence of abortion in insulin-dependent diabetes is at least as great in the general population, suggesting that there has been under-reporting in series to date.

Indeed, it might be that the increase in major malformations in the infants of insulin-dependent mothers might increase the spontaneous abortion

rate. The relatively small number of patients in this study has not permitted us to identify any particular reasons for any of the early abortions.

Experimental diabetes in rodents is associated with an excessive number of non-viable fetuses (Solomon, 1959) even though the number of implantation sites is unaffected (Eriksson *et al.*, 1982). This effect of maternal diabetes can be prevented by giving insulin (Ferret, Linden and Morgans 1950; Deucher, 1978). Though our diabetic patients were receiving conventional therapy, with once or twice daily insulin, and were not as poorly controlled as in these rodent experiments, HbA₁ levels were clearly elevated in many patients.

Our results have highlighted that diabetic control is poor in many insulin-dependent patients in the first trimester and suggests that a number of early abortions may be due to this factor. By the time a booking is made for antenatal care, it is usually too late to influence diabetic control at the critical time in the first trimester. Further efforts to improve control in the 6 weeks post-conception are required and we

hope will result from better pre-pregnancy counselling (Steel, Johnstone and Duncan, 1980). Such efforts could have beneficial effects in reducing spontaneous abortion and major congenital malformations in this group of patients.

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