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Risk of minor and major fetal malformations in diabetics with high haemoglobin A_{1c} values in early pregnancy

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Abstract

Maternal haemoglobin A_{1c} (HbA_{1c}) values were measured before the end of the 15th week of gestation in 142 pregnancies in women with insulin dependent diabetes. In pregnancies complicated by fetal malformations (n = 17) the mean initial HbA_{1c} value was 9·5 (SD 1·8)% of the total haemoglobin concentration, which was significantly ($p < 0·001$) higher than in pregnancies without malformations (8·0 (SD 1·4)%; n = 125). HbA_{1c} values did not differ between pregnancies complicated by minor and major fetal malformations, but the rate of malformations showed a positive relation to the HbA_{1c} value in early pregnancy ($\chi^2 = 11·9$; $p = 0·001$). Fetal malformations occurred in six out of 17 pregnancies (35·3%) in mothers whose initial HbA_{1c} value was 10% or more, in eight out of 62 pregnancies (12·9%) in mothers with initial values between 8·0% and 9·9%, and in only three out of 63 pregnancies (4·8%) in mothers with an initial value below 8·0%.

These data support the hypothesis that the increased incidence of fetal malformations in mothers with insulin dependent diabetes is associated with maternal hyperglycaemia during organogenesis. Hence diabetic women who are planning to have a child—especially those with a high HbA_{1c} value—should receive intensified metabolic control.

Introduction

The incidence of congenital malformations is about three times higher in infants of insulin dependent diabetic mothers than in the general population.[1] During recent years a dramatic decrease in both perinatal mortality and neonatal morbidity has occurred as a result of intensive treatment of diabetes during pregnancy. The incidence of congenital malformations, however, has remained essentially the same.[2] The exact cause of this increase in malformations in diabetic pregnancies is not known, but experimental[3] and clinical data[4] show an association between congenital malformations and maternal hyperglycaemia in early pregnancy—the critical period with regard to fetal malformations.[5]

We report an association between the severity of maternal hyperglycaemia in early pregnancy as measured by blood haemoglobin A_{1c} (HbA_{1c}) values and the occurrence of fetal malformations in mothers with insulin dependent diabetes.

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Patients and methods

Between April 1978 and December 1982 the maternal HbA_{1c} value had been determined at least once before the end of the 15th week of gestation in 139 insulin dependent diabetic patients who gave birth after 24 weeks of gestation. Four of them had a twin pregnancy. In addition, a fetal malformation was observed in three cases of induced abortion where an early HbA_{1c} determination had been carried out. In two of these cases preoperative ultrasound had detected the malformation. These cases were also included in the study, so that the total number of pregnancies was 142 and the total number of fetuses 146. The maternal diabetes was classified according to White, as modified by Pedersen.[6] Thirty eight pregnancies were in women with class B disease, 45 in women with class C disease, 49 in women with class D disease, and 10 in women with class F disease. The mean maternal age at delivery was 27·3 years (range 19-39).

Principles of the management of pregnancy and delivery of insulin dependent diabetics at this hospital have been described.[7] The patients were referred to the hospital between the sixth and 15th weeks of gestation and kept under the care of a specialist team of obstetricians and internists. Ultrasound examinations were performed to determine gestational age, number of fetuses, and fetal morphology and to monitor intrauterine growth. The infants were examined physically by neonatologists at least three times: at birth, at the age of 1 day, and on discharge from the hospital (not before seven days). If a congenital defect was found or suspected further diagnostic studies were carried out when necessary. Pregnancies were classified as (*a*) not complicated by malformation, (*b*) complicated by minor

malformation, and (c) complicated by major malformation. A malformation was classified as major if it was fatal or likely to cause serious handicap to the child. Other malformations were classified as minor (see table I).

HbA_{1c} was measured using the cation exchange method of Trivelli *et al*[8] with minor modifications.[9] The mean HbA_{1c} value in healthy pregnancies was 5·0 (SD 0·5)% of the total haemoglobin concentration throughout pregnancy.

HbA_{1c} values in groups with and without congenital malformations were compared using Student's unpaired *t* test. The relation of rate of malformation to HbA_{1c} values was assessed by the χ^2 test.

Results

A total 125 pregnancies were not complicated by fetal malformation. A malformed fetus or infant was observed in 17 pregnancies. In six cases the anomaly was classified as minor and in 11 cases as major (table I). The mean initial HbA_{1c} value was significantly higher in the group with minor malformations (9·3 (SD 1·9)%) and the group with major malformations (9·6 (SD 1·8)%) than in the group without malformations (8·0 (SD 1·4)%); $p<0·05$ and $p<0·001$, respectively. The difference in HbA_{1c} values between the groups with minor and major malformations was statistically not significant. In all 17 pregnancies complicated by a malformation the mean initial HbA_{1c} value was 9·5 (SD 1·8)%, which was significantly ($p<0·001$) higher than in the group without malformations.

There was a significant positive relation ($\chi^2=11·9$; $p=0·001$) between the maternal HbA_{1c} value in early pregnancy and the occurrence of malformations (table II). An initial HbA_{1c} value of 10·0% or more was associated with malformations in six out of 17 pregnancies (35·3%); two of these were minor (11·8%) and four major malformations (23·5%). An intermediate initial HbA_{1c} value (8·0-9·9%) was associated with malformations in eight out of 62 pregnancies (12·9%). Relatively low initial HbA_{1c} values—that is, below 8·0%—were associated with malformations in only three out of 63 pregnancies (4·8%).

Discussion

Leslie *et al* reported raised initial values of HbA_1 (total glycosylated haemoglobin) in three cases of severe fetal malformations occurring among 23 pregnancies in insulin dependent diabetic mothers. In 116 diabetic pregnancies in which the HbA_{1c} value was measured before the 14th week Miller *et al* observed 15 major anomalies.[4] The mean initial HbA_{1c} value was significantly higher in pregnancies complicated by major anomalies than in pregnancies with no anomalies. No minor malformations were reported.

Our results agree with those findings. In addition, we found an association between minor malformations and raised HbA_{1c} values in early pregnancy. This observation supports the hypothesis that during the first weeks of pregnancy, or possibly even before conception, maternal hyperglycaemia or other metabolic disturbances associated with hyperglycaemia may cause a large variety of malformations, ranging from minor and clinically insignificant to multiple and fatal. In our study fetal malformation was observed in 35% of pregnancies in which the initial HbA_{1c} value had been 10% or higher. This value is 10 SD above the mean during pregnancy in healthy controls.[9] A similar result was reported by Miller *et al*.[4] We emphasise, however, that owing to the methodological problems in measuring HbA_{1c}[11] each laboratory should establish its own reference values.

Studies on animals[3] show that the increase in congenital malformations in diabetic pregnancies may be prevented by strict control of diabetic metabolism during organogenesis. A similar result in man was reported by Fuhrmann *et al*.[12] They found only one malformation in the infants of 128 diabetic women subjected to scrupulous care before and during pregnancy. In 292 women of similar age and severity of diabetes and in whom strict control was begun only after eight weeks of gestation the number of malformed infants was 22 ($p<0·01$).

We have shown previously that a high maternal HbA_{1c} value during the second trimester of pregnancy signals a patient at special risk of perinatal death.[13] It seems that a high HbA_{1c} value in early pregnancy is associated with a clearly increased risk of fetal malformations. A diabetic woman of fertile age should be advised to avoid unplanned pregnancy. Measurement of HbA_{1c} is a simple way to determine whether a patient's diabetes is under satisfactory control before pregnancy. Whether an intensified treatment of diabetes to achieve an improved metabolic control will actually decrease the number of fetal malformations in these patients has still to be established.

TABLE I—*Fetal malformations, maternal age, and initial HbA_{1c} values in 142 diabetic pregnancies (White's classes B-F)*

Case No	Type of malformation	Maternal age (years)	White's class	Initial HbA_{1c} (%)
	Minor malformations			
1	Undescended testis (bilateral)	22	D	7·3
2	Undescended testis (unilateral)	28	D	8·1
3	Testicular hydrocele (unilateral)	26	B	8·2
4	Subluxation of hip (unilateral)	26	C	9·4
5	Hemivertebra (T7)	33	C	10·0
6	Single umbilical artery	28	C	12·7
	Major malformations			
7*	Hydrocephalus	27	B	7·3
8	Meningomyelocele (lumbar)	35	C	7·5
9†	Anencephaly	39	D	8·6
10†	Anencephaly	24	D	8·7
11	Cleft palate	22	C	9·0
12	Atresia of pulmonary valve (twin A)	27	C	9·0
13	Caudal regression syndrome	21	F	9·4
14†	Caudal regression syndrome	28	F	10·1
15	Agenesis of one kidney, supernumerary toe, hypoplastic thumb, anomalous lumbar spine	28	B	11·5
16	Large patent ductus arteriosus	31	B	12·0
17*	Aplasia of left diaphragm with hypoplasia of left lung, omphalocele	27	B	12·6

*Perinatal death. †Induced abortion.

TABLE II—*Distribution of diabetic pregnancies in relation both to maternal HbA_{1c} value before 16 weeks of gestation and to occurrence of fetal malformations*

Initial maternal HbA_{1c} value (%)	No (%) of pregnancies		
	No malformation	Minor malformation	Major malformation
⩾10·0	11 (64·7)	2 (11·8)	4 (23·5)
8·0-9·9	54 (87·1)	3 (4·8)	5 (8·1)
⩽7·9	60 (95·2)	1 (1·6)	2 (3·2)

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