

Glycosylated Haemoglobin as a Useful Index of Glucoregulation in the Management of Diabetic Pregnancy

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Diabetes in the mother is an important obstetric risk factor and is associated with high perinatal mortality rates. Control of diabetes in the preconceptional stage and early pregnancy is a crucial factor determining foetal congenital malformations (Mintz *et al.*, 1978). According to Pedersen's hypothesis, maternal hyperglycaemia causes increased delivery of glucose to the foetus with resultant stimulation of the foetal pancreas to secrete increased amount of insulin (Pedersen, 1977). The hyperinsulinaemia leads to foetal macrosomia with problems during delivery.

Several workers have stressed the value of good control of maternal blood sugar levels on outcome in diabetic pregnancies (Karlsson and Kjellmer, 1972; Essex *et al.*, 1973; Kitzmiller *et al.*, 1978). Definition of "good control" is difficult since criteria differ and must be defined by normal gestational standards and not by the usual non-gravid indices. Many clinicians still utilise the mean blood sugar level as an index of control. Karlsson and Kjellmer (*loc. cit.*) found a perinatal mortality rate of less than 4% when the mean blood sugar level was <100 mg.% during the 3rd trimester. Currently, the level of glycosylated haemoglobin (HbA₁) in the blood which reflects prior glucose levels has been suggested as a useful tool for monitoring glucoregulation in diabetes (Widness *et al.*, 1978; Kjaergaard and Ditzel, 1979; O'Shaughnessy *et al.*, 1979). Hence the present study was undertaken to evaluate the utility of monitoring HbA₁ levels in the management of diabetic pregnancy and to assess the effect of optimal maternal glucoregulation as indicated by maternal HbA₁ levels on the perinatal outcome.

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MATERIAL AND METHOD

The subjects studied were 17 pregnant women with well established preconceptional diabetes, 15 of them were non-insulin dependent (NIDDM) and 2 were insulin dependent (IDDM). According to White's classification (White, 1971) the 15 patients with NIDDM belonged to class B. The remaining 2 with IDDM were of the young onset type (onset below 19 years) with diabetes of less than 10 years duration. None of the patients had any renal or other complications.

Fasting and postprandial plasma glucose values and HbA₁ levels were measured at every antenatal visit to the diabetic clinic with an average of at least 2 determinations per trimester. Plasma glucose was measured by the orthotoluidine method (Hyvarinen and Nikkila, 1962). HbA₁ was determined colorimetrically by a modified method of Eross *et al.* (1981) and the values were expressed as percentage of total haemoglobin by using a regression formula.

Patients whose blood sugar levels were not well-controlled with diet alone were placed on a regimen of single daily injection of lente insulin or twice daily injections of soluble (plain) insulin.

RESULTS

Table 1 shows the individual clinical characteristics, the biochemical parameters studied and the outcome of pregnancy in all the 17 diabetic patients studied. The maternal age ranged from 20 to 37 years and the parity from 0 to 5. The duration of diabetes in these patients ranged from 1 to 6 years.

Fifteen out of a total of 17 patients (cases 1-15) showed good control of plasma sugar levels. Optimal control of blood glucose levels in this group was substantiated by the mean HbA₁ levels which measured $8.2 \pm 0.5\%$ (\pm SD), being comparable to the normal values of $6.5 \pm 0.8\%$ in non-diabetic women. The overall perinatal mortality was nil and the birth weights of the infants in this group were normal rang-

ing from 2.6 to 4.3 kg. with a mean of 3.3 ± 0.5 kg. (\pm SD). No congenital abnormalities or malformations were detected in any of these infants.

There was no incidence of any obstetric complications. Twelve out of the 17 patients were delivered by elective caesarean section. Five patients had normal deliveries of which one gave birth to a premature infant.

A comparison of the plasma glucose and HbA₁ levels and the outcome of pregnancy in the group of patients with optimal glucoregulation against those with significant hyperglycaemia are shown in Table 2.

Table 1—Showing Clinical Characteristics and the Outcome of Pregnancy

Case No.	Age (years)	Duration of diabetes	Mean plasma sugar (mg.%)		Mean HbA ₁ (%)	Outcome	
			Fasting	Postprandial		Nature of delivery	Birth weight of baby (kg.)
1	24	5	125	177	8.5	Caesarean section	3.5
2	29	1	120	121	7.8	"	4.0
3	25	4	127	173	7.8	Normal	3.2
4	32	1	107	171	8.5	Normal	3.4
5	25	1	94	149	8.3	Caesarean section	2.8
6	32	1	73	146	7.5	"	3.0
7	22	3	93	170	8.5	"	3.2
8	26	1	124	138	8.5	"	3.0
9	35	1	96	138	8.6	Normal	3.2
10	32	2	118	170	6.7	Caesarean section	4.3
11	37	1	91	170	7.8	"	2.6
12	26	4	127	186	8.5	"	3.5
13	31	4	105	144	8.6	"	3.2
14	29	1	102	151	8.4	"	2.8
15	26	1	110	150	8.2	"	3.4
16	20	6	230	240	9.5	Normal	2.5
17	20	2	132	200	9.8	Normal*	1.5

Case No. 1-15—NIDDM, No. 16-17—IDDM, * Premature infant of 32 weeks gestation

In 2 cases of IDDM (cases 16, 17) sub-optimal control of maternal hyperglycaemia was also indicated by a mean HbA₁ value of 9.5% and 9.8% for the 3 trimesters. There was no perinatal death in this group. However, poor diabetic control during the last trimester was an aetiological factor in the development of ketoacidosis and the birth of a low birth weight infant (2.5 kg) in one case and a premature delivery of a very low birth weight infant (1.5 kg) in another case.

DISCUSSION

No more important challenge faces the perinatologist than diagnosis and management of

Table 2—Showing Effect of Maternal Glucoregulation on the Outcome of Pregnancy

	Optimal diabetic control (15 cases)*	Poor diabetic control (2 cases)**	
	Mean \pm SD	Case 16	Case 17
Fasting plasma sugar (mg.%)	107 \pm 16	230	132
Postprandial plasma sugar (mg.%)	157 \pm 18	240	200
HbA ₁ (%)	8.2 \pm 0.5	9.5	9.8
Birth weight of baby (kg.)	3.3 \pm 0.5	2.5	1.5
Perinatal mortality	Nil		Nil
Maternal complication	Nil		Ketoacidosis

* Values given are mean \pm SD of the individual means for all 3 trimesters in this group

** Individual mean values for 3 trimesters

the diabetic pregnancy. Since the advent of insulin there has been a sharp decline in the maternal mortality but the perinatal mortality is still high (Gun, 1972; Naeye, 1979). Stringent control of maternal blood glucose level is absolutely necessary to obtain the best prognosis for the foetus and the mother (White, *loc. cit.*; Pedersen, *loc. cit.*).

There are no satisfactory means to assess maternal glucose control during pregnancy. The clinician has to rely on information obtained from urine examination and intermittent blood glucose measurements to assess the maternal metabolic control. Due to lowered renal threshold for sugar during pregnancy, urine sugar tests may not give a true picture of the metabolic control.

As glycosylated haemoglobin levels are related to time integrated blood glucose, HbA₁ estimation appears to be the best method currently available for assessing the quality of long term blood glucose control also during pregnancy (Widness *et al.*, *loc. cit.*; Kjaergaard and Ditzel, *loc. cit.*). The results of the present clinical studies also support this contention. There were no perinatal deaths or congenital foetal abnormalities in the group of pregnant diabetics studied, who were managed according to a simple plan based on early monitoring of diabetes control by blood glucose and HbA₁ levels and proper antenatal care.

The present results are also in agreement with the well-documented studies of Koenig *et al.* (1976) who have shown that there is an excellent correlation between HbA₁ levels and the blood sugar levels over the preceding 8 weeks in pregnant diabetics. It is observed in the present study that the perinatal outcome has been most favourable in the group of patients showing good diabetic control as indicated by HbA₁

levels. The opposite is also true of patients with poor diabetic control as shown by elevated HbA₁ values.

It is interesting to note that Widness *et al.* (*loc. cit.*) have reported direct correlations of maternal glucose levels with HbA₁ and subsequently of HbA₁ levels with infant birth weights. This, however, has not been confirmed by other workers (Miller *et al.*, 1979; Coen *et al.*, 1980). These data from the present study do indicate a favourable outcome in the birth weight of infants delivered by mothers with excellent diabetic control as shown by normal HbA₁ levels. Thus, repeated, determinations of HbA₁ in a pregnant diabetic can yield reliable information to the clinician on maternal diabetic control. HbA₁ measurements being simple and inexpensive can be carried out on an outpatient basis and can serve as an alternative to the more expensive management programmes such as home blood glucose monitoring or hospitalisation. Given the fact, that fasting, postprandial blood glucose levels and other glycaemic excursions after meals are all but momentary evaluations of a metabolic continuum, it is possible that HbA₁ which is a time-averaged assessment of prior glucose control may reflect better than any other measure of the degree of control. Thus, glycosylated haemoglobins have opened up some interesting possibilities to overcome the challenging problem of diabetic pregnancy.

SUMMARY

A study was undertaken to evaluate the utility of monitoring glycosylated haemoglobin (HbA₁) levels in the management of diabetic pregnancy. Fasting and postprandial plasma sugar and HbA₁ levels were determined (at least twice during each trimester) in 17 pregnant women with diabetes of 1 to 6 years duration before the onset of this pregnancy.

The perinatal outcome was most favourable in a group of 15 patients with NIDDM who showed good diabetic control as indicated by a mean (\pm SD) fasting plasma sugar of 107 ± 16 mg.%, mean (\pm SD) postprandial plasma sugar of 157 ± 18 mg.% and a mean (\pm SD) HbA₁ of $8.2 \pm 0.5\%$ in all 3 trimesters. There were no perinatal deaths or foetal congenital abnormalities detected in any of these 15 infants. The birth weight of these infants were normal ranging from 2.6 to 4.3 kg. with a mean (\pm SD) of 3.3 ± 0.5 kg. There was no incidence of any maternal or neonatal complication. Poor diabetic control in 2 patients with IDDM (mean HbA₁—9.5% and 9.8% respectively) resulted in the development of ketoacidosis and the deli-

very of a low birth weight infant (2.5 kg.) in one case and a premature infant of very low birth weight (1.5 kg.) in another case.

A significant correlation was observed between HbA₁ and the mean blood glucose levels over the preceding 8 weeks. Determination of HbA₁ level during each trimester can serve as an inexpensive means of obtaining reliable information on maternal glucoregulation for the successful management of diabetic pregnancy.

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