Maternal blood glucose control and outcome of diabetic pregnancy

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Summary

The results of management of 128 consecutive pregnancies occurring in diabetic patients who received insulin from before conception and throughout pregnancy are described. Mean maternal blood glucose levels were at least 1 mmol/litre greater than levels reported in normal pregnancy. Thirty-nine percent of the neonates had significant morbidity; respiratory distress syndrome (7.7%), hypocalcaemia (4.6%) and polycythaemia (10%) could be related to higher maternal blood glucose levels. Neonatal hypoglycaemia (9.2%), hyperbilirubinaemia (13.8%) and birth weight corrected for gestational age were not directly related to maternal blood glucose. This degree of maternal blood glucose control has reduced the large for dates infants (greater than 90th centile for gestational age) to 7%. Further reduction in the morbidity of infants of diabetic mothers requires studies of physiological maternal blood glucose levels which may not be possible with conventional insulin treatment as well as further efforts to reduce prematurity.

Introduction

Efforts made to control diabetes mellitus during pregnancy together with advances in obstetric and neonatal care have been associated with reduction of perinatal mortality to below 5%. In clinical practice it is not always possible with traditional methods of treatment and monitoring of diabetes to correct all metabolic abnormalities. During pregnancy in non-diabetic women (Gilmer *et al.*, 1975) blood glucose levels are kept within very narrow limits, the mean

diurnal venous plasma glucose being 4.69 mmol/litre $\pm$ 0.37 s.d. with a maximum plasma glucose of 6.29 mmol/litre $\pm$ 0.93 s.d. Capillary blood glucose would therefore rarely exceed 7.5 mmol/litre. For comparison in a detailed study (Peacock *et al.*, 1979) of day-to-day monitoring of capillary blood glucose during pregnancy an overall mean level of 7.1 mmol/litre $\pm$ 2.6 s.d. was achieved in 25 diabetic pregnancies with satisfactory outcome. However, at least 30% of the measurements were equal to or greater than 8 mmol/litre. Normal mean blood glucose levels can be achieved, either by intensive conventional therapy or by mechanical insulin infusion devices. To date such methods require considerable patient co-operation and staff supervision and the need for strictly normal metabolic control has not yet been established. Before making such a commitment we have analysed the results of a consecutive series of a relatively large number of insulin-dependent diabetic pregnancies to determine how high and variable the blood glucose is, using conventional insulin techniques, and to what extent blood glucose control may have affected the outcome.

Methods

One hundred and twenty-eight consecutive pregnancies delivered at 28 or more weeks gestation between 1974 and 1980 inclusive were managed in a standard manner. All patients had known diabetes and were receiving insulin at the time of conception. Forty-one pregnancies were in White's Class B (Hare and White, 1980), 44 in Class C, 39 in Class D and 4 in Classes R or F. Patients were seen fortnightly at a joint diabetic ante-natal clinic with non-fasting blood glucose being measured by an automated glucose oxidase method on capillary blood taken between

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09.30 and 10.30 hours. Urine was monitored by patients 4 times a day. Advice on diabetic control was freely available at all times.

After admission to hospital at 32–34 weeks' gestation, capillary blood glucose was measured at 09.30 hours (90 min after breakfast), 12 noon (immediately before lunch) and 15.30 hours on 3 days a week. Twice daily insulin was used with varying mixtures of a short acting insulin together with isophane insulin. There were no episodes of ketoacidosis. In 1974 delivery was planned at 36–37 weeks' gestation, but following the introduction of amniocentesis for lecithin/sphingomyelin (L/S) ratios (Gluck and Kulovich, 1973) in that year delivery has been after 37 weeks' gestation with L/S ratio equal to or greater than two. Delivery was earlier than 36 weeks in 21 of the 128 pregnancies, mainly on account of hypertension and concern for fetal welfare. Vaginal delivery was achieved in 52 pregnancies (41%), elective Caesarian section being performed in 30 pregnancies (23%) and emergency Caesarian section in 46 pregnancies (36%). The management of diabetes during labour and delivery has been described (Soler and Malins, 1978).

Two of the deliveries were twin pregnancies. Management of all 130 infants was standardized, babies being admitted to a special care unit and fed formula feeds 2 hourly if normal, or hourly if ill. Capillary blood glucose (Dextrostix) was monitored 3 hourly for the first 24 hr of life and hypoglycaemia (less than 1.5 mmol/litre) confirmed on venous blood. Respiratory distress syndrome was diagnosed if onset of respiratory difficulty occurred within 6 hr of birth and persisted for 48 hr. Hyperbilirubinaemia was defined as a plasma bilirubin equal to or greater than 250 μ mol/litre, hypocalcaemia as plasma calcium less than 1.8 mmol/litre and polycythaemia as haemoglobin greater than 18 g/dl. Birth weight centiles were taken from the data of Gairdner and Pearson (1971).

Maternal blood glucose data has been analysed by calculating a mean for the different times of measure-

ment in each individual pregnancy and using these figures to obtain group means. The variation in blood glucose data has been expressed as standard deviations.

Results

The mean morning blood glucose level measured in out-patients was 7.2 mmol/litre (Tables 1 & 2) with 43% of results being above 7.5 mmol/litre. The corresponding measurement when an in-patient was greater at 7.9 mmol/litre ($P < 0.01$ paired *t*-test) with 54% of levels above 7.5 mmol/litre. The pre-lunch and mid-afternoon blood glucose levels were lower than the post breakfast levels and all the in-patient results tended to be less variable than the out-patient results.

Relating out-patient maternal blood glucose control to neonatal morbidity (Table 3) the levels were significantly higher in those infants subsequently developing respiratory distress syndrome and hypocalcaemia. This was not seen in the corresponding in-patient data for the group with the respiratory distress; the hypocalcaemic neonates were too few to assess statistically. Neonatal polycythaemia was associated with higher in-patient maternal blood glucose levels. Mean maternal blood glucose levels showed no relationship to neonatal hypoglycaemia (Table 3) or to centile birth weight (Table 4). In those delivered at 36 or more weeks' gestation there was no correlation of actual birth weight with either in-patient 09.30 hours blood glucose ($r = -0.09$) or mean in-patient blood glucose ($r = -0.03$). There was no apparent greater variation (s.d.) or percentage blood glucose levels greater than 7.5 mmol/litre in the mothers of neonates with morbidity or in the mothers of small or large for dates infants. The distribution of centile birth weight was similar when subdivided into White's classes with no excess of small for dates infants in class D and R.

In the nine pregnancies (7%) with polyhydramnios which was not associated with a major congenital

TABLE 1. Maternal blood glucose concentrations as out-patient

No. pregnancies	128		
No. days measured/ pregnancy (mean $\pm$ s.d.)	12.6 $\pm$ 3.2		
Blood glucose (mmol/litre)	Mean	Mean s.d.	% observations > 7.5
09.30 hours	7.2	3.3	43

The mean was calculated from the mean blood glucose for an individual pregnancy.

The % of blood glucose levels greater than 7.5 mmol/litre was similarly derived.

TABLE 2. Maternal blood glucose concentrations as in-patient

No. pregnancies No. days measured/ pregnancy (mean $\pm$ s.d.) Blood glucose (mmol/litre)	Gestational age at delivery (weeks)					
	<36			>36		
		21		107		
	Mean	11.8 $\pm$ 6.2 Mean s.d.	% observ. >7.5	Mean	14.3 $\pm$ 5.6 Mean s.d.	% observation >7.5
09.30 hours	8.0	2.5	56	7.9	2.2	54
12.00 hours	5.4	2.4	18	5.0	2.0	14
15.30 hours	6.0	2.3	28	5.0	1.8	15

The mean was calculated from the mean blood glucose for an individual pregnancy.

The % of blood glucose levels greater than 7.5 mmol/litre was similarly derived.

TABLE 3. Neonatal morbidity in relation to maternal blood glucose concentrations (mmol/l)

	nil	Respiratory distress	Hypocalcaemia	Polycythaemia	Hypoglycaemia	Hyperbilirubinaemia*
Out-patient (128 pregnancies) mean $\pm$ s.d.	7.0 $\pm$ 1.6	8.7 $\pm$ 1.7 $P < 0.01$	8.9 $\pm$ 1.7 $P < 0.01$	7.3 $\pm$ 1.9	7.5 $\pm$ 1.6	7.3 $\pm$ 1.7
n(%)	78(61)	10(7.7)	6(4.6)	13(10)	12(9.2)	18(13.8)
In-patient (107 pregnancies) (delivered 36 or more weeks) (mean $\pm$ s.d.)						
09.30 hours	7.8 $\pm$ 1.4	8.2 $\pm$ 1.1	9.1	8.5 $\pm$ 1.5 $P < 0.05$	7.1 $\pm$ 2.2	8.4 $\pm$ 1.5
12.00 hours	4.8 $\pm$ 1.1	5.3 $\pm$ 1.1	5.4	5.4 $\pm$ 1.0 $P < 0.05$	5.2 $\pm$ 2.2	5.5 $\pm$ 0.9 $P < 0.02$
15.30 hours	4.8 $\pm$ 1.1	5.8 $\pm$ 1.2	7.5	5.8 $\pm$ 0.9 $P < 0.01$	4.4 $\pm$ 2.3	5.2 $\pm$ 0.9
n(%)	71(66)	7(6.5)	3(2.8)	10(9.3)	10(9.3)	17(15.9)

*excluding one infant with Rhesus haemolytic disease.

P values in comparison with neonates with no morbidity (unpaired *t*-test)

abnormality in the fetus, the maternal blood glucose levels (mean $\pm$ s.d. out-patients 6.9 $\pm$ 0.9, in-patients 09.30 hours, 7.2 $\pm$ 1.3, 12.00 hours, 4.6 $\pm$ 1.2 and 15.30 hours, 4.1 $\pm$ 1.3 mmol/litre) were not different from the whole group. The 11 pregnancies (9%) with hypertension had similar maternal blood glucose levels as an out-patient (mean $\pm$ s.d. 7.4 $\pm$ 1.6 mmol/litre) but the in-patient data was incomplete as the majority were delivered before 36 weeks.

One typical diabetic stillbirth occurred where blood glucose control had been relatively poor in the last trimester (mean $\pm$ s.d. out-patient 6.9 $\pm$ 4.3, in-patient 09.30 hours, 11 $\pm$ 2.5, 12.00 hours, 8.1 $\pm$ 3.9, 15.30 hours, 7.4 $\pm$ 2.7 mmol/litre).

Discussion

Significant perinatal morbidity and mortality persists among the infants of diabetic mothers in our series but the extent that failure of strict diabetic control contributes to these perinatal problems is answered only in part.

Conventional insulin techniques in the insulin-

dependent patient rarely restore the blood glucose levels throughout 24 hr to the levels found in non-diabetic subjects. The choice of an upper limit of 7.5 mmol/litre is derived from reported studies on non-diabetic pregnancy (O'Sullivan *et al.*, 1974) and represents the extreme upper limit of the normal range. No patient in our series had all measurements of capillary blood glucose below this upper limit. The percentage of results above this level was similar to a series where detailed home monitoring of blood glucose was used (Peacock *et al.*, 1979). All our out-patient and in-patient mean blood glucose levels are at least 1 mmol/litre greater than corresponding levels in non-diabetic pregnancy (Stubbs *et al.*, 1980) and much more variable as shown by the greater standard deviations.

In a similar series to ours (Leveno *et al.*, 1979) approximately one-half of the neonates had some morbidity which was unrelated to pre-prandial maternal blood glucose levels. Our finding of 39% morbidity is comparable but our level of control has eliminated large for dates infants. We were unable to confirm any correlation of blood glucose with birth

TABLE 4. Blood sugar concentrations in relation to birth weight (mmol/l)

	Centile birth weight in singleton pregnancies			
	<10	10-50	50-90	>90
Out-patient (126 pregnancies)				
mean $\pm$ s.d.	7.0 $\pm$ 1.6	7.4 $\pm$ 1.6	7.2 $\pm$ 2.1	7.5 $\pm$ 1.0
n(%)	20(16)	60(48)	38(30)	8(6)
In-patient (107 pregnancies)				
(delivered 36 weeks or more)				
mean $\pm$ s.d.				
09.30 hours	8.3 $\pm$ 1.0	7.8 $\pm$ 1.5	7.9 $\pm$ 1.5	7.4 $\pm$ 1.5
12.00 hours	5.2 $\pm$ 0.9	5.0 $\pm$ 1.1	4.9 $\pm$ 1.0	4.8 $\pm$ 1.1
15.30 hours	5.2 $\pm$ 1.1	4.8 $\pm$ 1.1	5.5 $\pm$ 1.4	4.7 $\pm$ 1.0
n(%)	16(15)	52(48)	31(30)	8(7)

weight as reported by Kitzmiller *et al.* (1978), but in their series comparable blood glucose levels were approximately 1 mmol/litre higher than ours and slightly more than one-third of all neonates were large for gestational age. Our results suggest that maternal blood glucose control is significantly related to the development of respiratory distress syndrome, hypocalcaemia and polycythaemia. Whether stricter diabetic control would eliminate neonatal hypoglycaemia or hyperbilirubinaemia cannot be answered by these results.

Careful diabetic control, however, together with current obstetric management has eliminated many of the problems of diabetic pregnancy. Many infants do not require special care facilities; severe cases of respiratory distress are not seen and the typical large for dates infant is a rarity.

Concern about the unexplained diabetic stillbirth and placental insufficiency has hitherto determined the policy of early delivery. The one diabetic stillbirth in this series occurred in a mother whose diabetes was relatively poorly controlled. The policy of delivering at term must depend on balancing the advantages of maturity against these risks but the level of maternal blood glucose control needed to avoid these complications from 37 weeks gestation to term is not yet known. Neonatal morbidity was no less in a series where the policy of elective pre-term delivery was abandoned (Lemons, Vargas and Delaney, 1981).

It is encouraging that newer insulin infusion systems may be useful in diabetic pregnancy, particularly in avoiding hypoglycaemia which is a constant concern with bolus injections. However, with present techniques of subcutaneous infusion the mean level and variation in blood glucose are not necessarily restored to those found in non-diabetic subjects (Potter, Reckless and Cullen, 1980). Intensive conventional therapy with multiple insulin injections (Jovanovic *et al.*, 1980) may prove to be more acceptable and a more effective method of treatment for diabetic pregnancy.

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