Neonatal hypoglycaemia in infants of insulin-dependent diabetic mothers

F. I. R. MARTIN, G. W. DAHLENBURG, JOAN RUSSELL, and P. JEFFERY

From the Diabetic Clinic, Royal Women's Hospital, Carlton, Melbourne; and the Endocrine and Biochemistry Departments, Royal Melbourne Hospital, Australia

Martin, F. I. R., Dahlenburg, G. W., Russell, J., and Jeffery, P. (1975). *Archives of Disease in Childhood*, 50, 472. **Neonatal hypoglycaemia in infants of insulin-dependent diabetic mothers.** Neonatal hypoglycaemia (blood glucose <20 mg/100 ml) occurred in the first 6 hours of life in 25 of 34 infants born to diabetic mothers receiving insulin. Despite severe hypoglycaemia (blood glucose <10 mg/100 ml) in 17, clinical features of hypoglycaemia were absent in all but 2. Hypoglycaemia was not related either to the level of plasma insulin in cord blood, determined as nonextracted immunoreactive insulin, or to the degree of control of maternal blood glucose during pregnancy. The frequent occurrence of severe neonatal hypoglycaemia in the infants born to diabetic mothers receiving insulin appears to be due rather to failure to maintain basal glucose homeostasis after birth than to hyperinsulinism.

Infants of diabetic mothers requiring insulin are liable to develop severe hypoglycaemia in the first few hours of life more frequently than infants of comparable gestation or weight born to normal mothers or to mothers whose diabetes does not require insulin during pregnancy (McCann *et al.*, 1966; Isles, Dickson, and Farquhar (1968; King *et al.*, 1969). This severe neonatal complication has been attributed to hyperinsulinaemia on the basis both of more rapid glucose assimilation (Baird and Farquhar, 1962; McCann *et al.*, 1966; Isles *et al.*, 1968; Molsted-Pedersen, 1972) and of increased plasma insulin response to glucose (Baird and Farquhar, 1962; Jorgenson *et al.*, 1966; Isles and Farquhar, 1967). Confirmation of this hypothesis has been inconclusive due to the transplacental passage of maternal insulin antibodies which interfere with the immunoassay of insulin.

Method of study

Thirty-four infants born to mothers with insulin-requiring diabetes attending the Diabetic Clinic at the Royal Women's Hospital were studied. The diabetic mothers were seen every 2 or 3 weeks during pregnancy and were routinely hospitalized at 34 weeks, 2 to 3 weeks before expected delivery. Attempts were made to maintain relatively normoglycaemic diabetic control

by the use of insulin and diet during the whole of the pregnancy and both in and out of the hospital. Blood glucose estimations were routinely performed at 11 a.m., 3.30 p.m., and 8.00 a.m. The degree of diabetic control was assessed by determining the mean blood glucose for each subject, both as an outpatient at clinic visits and when admitted to hospital. The number of blood glucose estimations varied. 29 patients had more than 20 estimations from the clinic (mean 27, range 6–50), and 30 out of 33 women in hospital before delivery had more than 10 (mean 22, range 6–86).

Delivery was either by vaginal route after induction of labour or by caesarean section. At delivery cord blood was obtained for assay of plasma immunoreactive insulin and insulin antibodies. Blood glucose was measured hourly on venous blood for the first 6 hours and then every 4 to 6 hours till 48 hours. The infants were fed glucose orally from 2 hours. Hypoglycaemia (blood glucose <20 mg/100 ml) whether manifest clinically or asymptomatic was immediately treated with intramuscular glucagon and intravenous dextrose infusion. In some infants blood was collected daily for the first 10 days and, in others, less frequently up to 6 months after delivery for serial assays of immunoreactive insulin and insulin antibodies.

Total plasma immunoreactive insulin was assayed by a dextran-charcoal assay and insulin antibody was estimated as a percentage binding of added ¹²⁵I-insulin to plasma determined by dextran-charcoal (Pearson and Martin, 1970). Dilution of plasma for assay of insulin in diabetic patients with insulin antibodies has been

Received 25 November 1975.

described elsewhere (Martin and Russell, 1974). Using 0.2 ml plasma, duplicate assays of nonextracted insulin were found to be reproducible and a straight-line relation was found between different dilutions of plasma. Blood glucose was measured by autoanalyser using a glucose oxidase method. The accuracy of this method was $\pm 4\%$, but below 10 mg/100 ml there was variation in the parallelism of samples and standards. For this reason infants were grouped as having a lowest blood glucose recorded of <10 mg/100 ml, 10–20 mg, or >20 mg.

Results

Thirty-four infants born to diabetic mothers requiring insulin were studied. The mothers had a mean age of 26.9 years (range 20–42 years) and duration of diabetes mellitus was from 0.2 to 24 years (mean 10.8 years). Insulin requirements at delivery were between 24 and 124 units/day. Gestation was estimated at 36 to 37 weeks in the majority, but 6 infants were delivered at between 35 and 36 weeks, 3 at 37 to 38 weeks, and one at 33 weeks. One-half were delivered vaginally and the other half by lower-segment, caesarean section, there being no relation between any of the results and method of delivery. Birthweight was between 1729 and 4919 g (mean $3383 \text{ g} \pm 583 \text{ SD}$); placental weight was increased (mean $692 \text{ g} \pm 198 \text{ SD}$, range 400–1500 g) and was significantly related to birthweight ($r = 0.69$, $P = <0.001$). Birthweight was significantly inversely correlated with the duration of the mother's diabetes ($r = -0.42$, $P = <0.02$), but the correlation between duration and placental weight was not significant.

From all infants adequate blood glucose measurements in the first 24 hours were available for assessment. In 17 the lowest blood glucose recorded in the first 6 hours of life was <10 mg/100 ml; in 8 it was between 10 and 20 mg/100 ml, and in 9 >20 mg. Only 2 infants had clinical features of cerebral irritability and twitching suggestive of hypoglycaemia. There was no difference in birthweight, placental weight, maternal age, duration of diabetes, or insulin dose between the hypoglycaemic and normoglycaemic infants.

In cord blood the estimated total plasma insulin (nonextracted immunoreactive) was between 26 and 1887 $\mu\text{U/ml}$ and the insulin antibody titre, estimated as percentage binding ^{125}I -insulin, was between 0 and 39%; plasma insulin was related to ^{125}I -insulin binding ($r = 0.66$, $P = <0.001$), but not to neonatal blood glucose levels (Fig. 1). In 5 infants in whom antibody binding of ^{125}I -insulin was normal (<4%), plasma insulin in cord blood was 37, 140, 26, 47, and 147 $\mu\text{U/ml}$ (mean $72.0 \mu\text{U/ml}$). In 3 of these infants severe hypoglycaemia occurred

FIG. 1.—Nonextracted plasma insulin (NE) in cord blood of 34 infants born to diabetic mothers requiring insulin compared with the lowest blood glucose recorded in the first 6 hours of life.

(blood glucose <10 mg/100 ml) which did not correlate with either plasma insulin or insulin dose. In 11 gestational diabetics also studied who had never received insulin, the plasma insulin of cord blood was between 14 and 92 $\mu\text{U/ml}$ (mean $35.6 \pm 23.8 \text{ SD}$), and in 21 infants of normal mothers studied by the same method, immunoreactive insulin of cord blood had a mean value of $24.4 \pm \text{SD } 10.6 \mu\text{U/ml}$ with an observed range of 11–47 $\mu\text{U/ml}$. Percentage binding of ^{125}I -insulin was less than 4% in all the children of gestational diabetics or normal mothers.

Blood glucose control both in the clinic and in the ward before delivery varied widely but was unrelated to birthweight, placental weight, maternal age, or duration of diabetes. The severity of neonatal hypoglycaemia was not related to the control of the mother's diabetes as expressed by mean blood glucose either in the clinic or in the ward before delivery (Fig. 2 and 3). 4 women had well controlled diabetes throughout (mean outpatient blood glucose 108, 89, 113, 104 mg/100 ml; mean inpatient blood glucose 86, 112, 66, 79 mg/100 ml); in all of their infants blood glucose fell below 20 mg, and below 10 mg in 3. Further, there was no relation between the mother's diabetic control during pregnancy as assessed by mean blood glucose and plasma insulin of cord blood. Little change in plasma insulin occurred up to 5 days after birth, but in 5 children in whom serial blood samples were assayed for

FIG. 2.—Mean blood glucose in mg/100 ml at antenatal outpatient clinic visits of 34 insulin-requiring diabetic women compared with the lowest blood glucose recorded in their children during the first 6 hours of life.

FIG. 3.—Mean blood glucose in mg/100 ml during in-patient ward assessment before delivery of 33 insulin-requiring diabetic women compared with the lowest blood glucose recorded in their children during the first 6 hours of life.

plasma insulin for up to 6 months, both plasma insulin and percentage binding decayed in parallel, with an estimated half-time of approximately 22 days.

Discussion

The present investigation has confirmed previous reports (McCann *et al.*, 1966; Isles *et al.*, 1968; King *et al.*, 1969; Bloom and Johnston, 1972) that severe neonatal hypoglycaemia in infants of diabetic mothers receiving insulin is common, but in contrast to the experience of Francois *et al.* (1974) hypoglycaemia did not persist beyond the first day of life. Hypoglycaemia was unrelated either to the estimated level of circulating immunoreactive insulin or to any other infant parameter. The method used to measure immunoreactive insulin by dilution in the presence of insulin antibodies (non-extracted immunoreactive insulin) has been shown to provide a constant estimate of 60% of 'total' immunoreactive insulin as determined by acid-alcohol extraction, and is related to the 'free' fraction of immunoreactive insulin as determined by alcohol precipitation (Heding, 1972; Martin and Russell, 1974). It is not possible to reproduce by an *in vitro* method the kinetics of dissociation of the antigen-antibody complex which occurs in the body so that any measurement of immunoreactive insulin in the presence of insulin antibodies remains only an estimate of the effective level of plasma immunoreactive insulin. In a few cases where it was determined there was agreement between plasma insulin and ^{125}I -insulin binding in both cord blood and maternal blood; thus it appears that plasma insulin in cord blood is largely maternal in origin. In the 5 children of insulin-requiring mothers who showed no evidence of insulin antibody formation as judged by normal levels of ^{125}I -insulin binding, immunoreactive insulin approached the level in gestational diabetics. Francois *et al.* (1974) have recently published similar results to ours. Using a double antibody method they obtained similar estimates of total insulin in the cord blood of babies born to insulin-dependent diabetic mothers. The incidence of neonatal hypoglycaemia was similar in children of insulin dependent and gestational diabetics and from their figures there was no correlation between cord insulin and neonatal blood sugar. Cord blood immunoreactive insulin levels were similar in gestational diabetics and antibody negative insulin-dependent diabetics, both being higher than controls.

The concept that maternal hyperglycaemia is the cause of the hyperplasia of the β cells of the islets seen in the diabetic infant with subsequent hyperinsulinaemia is not new (King *et al.*, 1969). Several investigators have shown both an increased response of immunoreactive insulin and a faster glucose disappearance rate following an acute intravenous glucose load in children of insulin-

requiring diabetics compared with gestational diabetics or controls (Baird and Farquhar, 1962; Jorgenson *et al.*, 1966; Isles and Farquhar, 1967; Isles *et al.*, 1968; Molsted-Pedersen, 1972). This does not explain the more frequent and severe spontaneous fall in blood glucose observed in the first few hours of life, and King *et al.* (1969), comparing insulin release and glucose tolerance to increasing glucose loads, obtained contrary results. Similarly, no relation between glucose and plasma immunoreactive insulin was found in infants of gestational diabetics (Obenshain *et al.*, 1969). The present investigation has also shown no relation between the degree of the maternal hyperglycaemic stimulus, which ranged from near normal to very abnormal, and either neonatal blood sugar or cord insulin level. The recent description (Nakagawa *et al.*, 1973) of hypoglycaemia (attributed to antigen-antibody release) in infants born to a mother with 'idiopathic' insulin antibodies and raised plasma immunoreactive insulin is of great interest. However, hypoglycaemia was not severe and tended to persist, in contrast to the acute hypoglycaemia observed in the infants of diabetic mothers.

The sensitivity to insulin in term infants appears to be less than would be expected in normal adults (Bowie, Mulligan, and Schwartz, 1963). Severe insulin insensitivity is present in anencephalic infants (Hayek, Driscoll, and Warshaw, 1973) and preterm infants have been shown to be both less sensitive to intravenous tolbutamide than term babies and to have no fall in blood glucose after arginine-stimulated insulin release (Cornblath, Wybregt, and Baens, 1963; Grasso *et al.*, 1973). Bloom and Johnston (1972) showed that plasma pancreatic glucagon as determined by radioimmunoassay using a relatively specific antiserum increased less in response to blood glucose fall 2 hours after birth in infants of both gestational and insulin treated diabetics than 'small-for-dates' infants. Whether this apparent difference in the diabetic neonate is enough to explain hypoglycaemia requires further evaluation. In the present series it was noted that in none of the 3 infants who developed respiratory distress syndrome did the blood glucose fall below 20 mg/100 ml. This may agree with the recent report that hypoxia is a much stronger stimulus to increase neonatal hepatic glucose output than hypoglycaemia (Hetenyi, Cowan, and Varma, 1973).

The maintenance of normal blood glucose during fasting is dependent upon an adequate supply of endogenous substrate (i.e. amino acids, lactate, glycerol), a functionally intact enzyme system in the liver to promote glycolysis and gluconeogenesis, and

an integrated endocrine regulation of these processes (Pagliara *et al.*, 1973). The human infant at birth has a limited supply of hepatic glycogen, and as about 50% of new glucose production is normally derived from protein stores and the relative protein mass is significantly smaller than the adult, it may be that these sources of gluconeogenesis are inadequate in the infant of the diabetic mother. Although qualitative differences in the enzyme content of the placentas of diabetic patients have been described (Gabbe *et al.*, 1972), there seems to be no information concerning the activity and concentration of hepatic and renal glycolytic or gluconeogenic enzymes in the infants of diabetic mothers.

The possibility that abnormalities in the induction, activity, or concentration of glycogenolytic and/or gluconeogenic enzymes and not hyperinsulinism are the determinants of neonatal hypoglycaemia in infants of diabetic mothers requires further investigation.

The assistance of Dr. I. Horachek, Biochemistry Department, Royal Women's Hospital, and Mrs. A. Murphy is gratefully acknowledged.

REFERENCES

- Baird, J. D., and Farquhar, J. W. (1962). Insulin-secreting capacity in newborn infants of normal and diabetic women. *Lancet*, **1**, 71.
- Bloom, S. R., and Johnston, D. I. (1972). Failure of glucagon release in infants of diabetic mothers. *British Medical Journal*, **4**, 453.
- Bowie, M. D., Mulligan, P. B., and Schwartz, R. (1963). Intravenous glucose tolerance in the normal newborn infant. The effects of a double-dose of glucose and insulin. *Pediatrics*, **31**, 590.
- Cornblath, M., Wybregt, S. H., and Baens, G. S. (1963). Studies of carbohydrate metabolism in the newborn infant, tests of carbohydrate tolerance in premature infants. *Pediatrics*, **32**, 1007.
- Francois, R., Picaud, J. J., Ruitton-Ugliengo, A., David, L., Cartal, M. J., and Bauer, D. (1974). The newborn of diabetic mothers. *Biology of the Neonate*, **24**, 1.
- Gabbe, S. G., Demers, L. M., Greep, R. O., and Vilee, C. A. (1972). Placental glycogen metabolism in diabetes mellitus. *Diabetes*, **21**, 1185.
- Grasso, S., Messina, A., Distefano, G., Vigo, R., and Reitano, G. (1973). Insulin secretion in the premature infant; response to glucose and amino acids. *Diabetes*, **22**, 349.
- Hayek, A., Driscoll, S. G., and Warshaw, J. B. (1973). Endocrine studies in anencephaly. *Journal of Clinical Investigation*, **52**, 1636.
- Heding, L. G. (1972). Determination of total serum insulin (IRI) in insulin-treated diabetic patients. *Diabetologia*, **8**, 260.
- Hetenyi, G., Cowan, J. S., and Varma, S. (1973). Glucose homeostasis in the newborn dog. *8th Congress International Diabetes Federation*, p. 145, abstr. 314. Excerpta Medica, Amsterdam.
- Isles, T. E., and Farquhar, J. W. (1967). The effect of endogenous antibody on insulin-assay in the newborn infants of diabetic mothers. *Pediatric Research*, **1**, 110.
- Isles, T. E., Dickson, M., and Farquhar, J. W. (1968). Glucose tolerance and plasma insulin in newborn infants of normal and diabetic mothers. *Pediatric Research*, **2**, 198.
- Jorgenson, K. R., Deckert, T., Molsted-Pedersen, L., and Pedersen J. (1966). Insulin, insulin-antibody and glucose in plasma of newborn infants of diabetic women. *Acta Endocrinologica*, **52**, 154.

- King, K. C., Adam, P. A. J., Clemente, G. A., and Schwartz, R. (1969). Infants of diabetic mothers: attenuated glucose uptake without hyperinsulinemia during continuous glucose infusion. *Pediatrics*, **44**, 381.
- McCann, M. L., Chen, C. H., Katigbak, E. B., Kotchen, J. M., Likly, B. F., and Schwartz, R. (1966). Effects of fructose in hypoglycemia in infants of diabetic mothers. *New England Journal of Medicine*, **275**, 1.
- Martin, F. I. R., and Russell, J. (1974). A simple method for determining plasma insulin in the presence of endogenous insulin antibodies. *Diabetologia*, **10**, 93.
- Molsted-Pedersen, L. (1972). Aspects of carbohydrate metabolism in newborn infants of diabetic mothers. *Acta Endocrinologica*, **69**, 174.
- Nakagawa, S., Suda, N., Kudo, M., and Kawasaki, M. (1973). A new type of hypoglycemia in a newborn infant. *Diabetologia*, **9**, 367.
- Obenshain, S. S., Adam, P. A. J., King, K. C., Teramo, K., Raivio, K. O., Raiha, N., and Schwartz, R. (1969). Human fetal insulin response to sustained maternal hyperglycaemia. *New England Journal of Medicine*, **283**, 566.
- Pagliara, A. S., Karl, I. E., Haymond, M., and Kipnis, D. M. (1973). Hypoglycemia in infancy and childhood. *Journal of Pediatrics*, **82**, 365.
- Pearson, M. J., and Martin, F. I. R. (1970). The separation of total plasma insulin from binding proteins using GEL filtration; its application to the measurement rate of insulin disappearance. *Diabetologia*, **6**, 581.

Correspondence to Dr. F. I. R. Martin, Department of Endocrinology, Royal Melbourne Hospital, Melbourne, Victoria 3050, Australia.