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Postnatal Glucose Kinetics in Newborns of Tightly Controlled Insulin-Dependent Diabetic Mothers

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ABSTRACT. Infants of diabetic mothers are at risk of developing hypoglycemia postnatally. Strict control of blood glucose during pregnancy might result in adequate glucose homeostasis in the neonate. We followed 15 mother-infant pairs from the beginning of pregnancy until birth. Glucose kinetics in the infants were measured on the first day of life, using a stable isotope dilution technique. Furthermore, levels of alternative substrates, FFA, and ketone bodies were measured. All infants received i.v. glucose from birth onward at a rate of 3.4 ± 0.7 mg/kg/min (mean ± SD). There was no relationship between the parameters of control of the insulin-dependent diabetes mellitus in the mothers and glucose kinetics in their infants. Glucose turnover was 5.2 ± 1.1 mg/kg/min, glucose production rate (GPR) was 1.8 ± 1.1 mg/kg/min. GPR was significantly lower in the infants studied at the end of the first day of life ($p < 0.01$), irrespective of the glucose infusion rate. Furthermore, the lower GPR was associated with an increased concentration of ketone bodies, suggesting an increased production of ketone bodies in these infants. The relatively high GPR measured in the infants who were studied in the first hours postnatally may be the result of postnatal hormonal stimulation of glycogenolysis and/or gluconeogenesis. From this study, we conclude that glucose kinetics in infants of tightly controlled diabetic mothers appear to be normal. Interestingly, despite the near-optimal insulin therapy in the mothers, there is a relationship between the SD scores of birth weight and the mean 3rd-trimester blood glucose values. (*Pediatr Res* 34: 443–447, 1993)

Abbreviations

3OHB, 3-hydroxy butyrate
GPR, glucose production rate
GIR, glucose infusion rate
GsHb, glycosylated Hb
MPE, mole percent excess
Ra, glucose appearance rate
SD score, standard deviation score

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Infants of diabetic mothers are prone to hypoglycemia during the first hours after birth (1–3). Suboptimal control of diabetes mellitus during pregnancy, resulting in maternal and fetal hyperglycemia, appears to be a major factor causing disturbances in neonatal glucose homeostasis including neonatal hyperinsulinemia (4) and an impairment of the postnatal glucagon surge (5).

Management of diabetes during pregnancy has changed dramatically during the past decade with the refinement of insulin administration (such as multiple-dose regimens, and continuous s.c. insulin infusion) and the use of the daily blood glucose monitoring. Differences in control of diabetes during pregnancy might explain the apparent differences between the results of the few studies measuring glucose kinetics in infants of diabetic mothers shortly after birth. Kalhan *et al.* (6) found significantly lower glucose production rates in infants of diabetic mothers suggesting impaired glycogenolysis and/or gluconeogenesis. King *et al.* (7) and Cowett *et al.* (8), however, did not find lower glucose production rates in infants of diabetic mothers compared with control infants. These studies did not give details about the control of diabetes during pregnancy except for the mothers' level of GsHb at delivery in the study reported by Cowett *et al.* (8). The pregnant diabetic women in that study had higher concentrations of GsHb compared with the nondiabetic pregnant women (9).

Therefore, we conducted this study of mother-infant pairs, where the maternal diabetes was tightly controlled, aiming at normal blood glucose and GsHb concentrations. The women were monitored from the beginning of pregnancy until birth of their infant. Glucose kinetics in the infants were measured within the first day of life.

SUBJECTS AND METHODS

Mothers. The study contained 15 mother-infant pairs. Data concerning the severity of diabetes are listed in Table 1. The insulin-dependent diabetes was regulated with continuous s.c. insulin infusion in nine women; six women were on split-dose therapy. Self-monitoring of blood glucose concentrations was performed daily by finger-prick sampling of capillary blood. Once a week, a 24-h blood glucose profile was made throughout pregnancy. Measurements were obtained at 0300 h, 0700 h (fasting), 1.5 h after breakfast, 1100 h, 1.5 h after lunch, 1700 h, 1.5 h after dinner, and finally at 2300 h. Insulin administration was adjusted according to the blood glucose values. A mean trimester blood glucose value was derived from the means of all weekly 24-h blood glucose measurements.

The GsHb level was determined every other week throughout pregnancy. The mean trimester GsHb level was calculated from all GsHb values obtained during a particular trimester.

Infants. Nine infants were delivered by cesarean section; the

Table 1. *Classification of diabetes according to White, route of insulin administration, mean trimester GsHb level during each trimester of pregnancy and at delivery, and the mean trimester blood glucose values of 15 pregnant diabetic women and gestational age, birth weight, SD score of birth weight, and GsHb level of their infants**

Mother /infant	White class	Insulin administration	Mean trimester GsHb level (%)				Mean trimester blood glucose level (mmol/L)			Gestational age (wk)	Birth wt (kg)	SD score	GsHb (%)
			1st	2nd	3rd	At delivery	1st	2nd	3rd				
1	C	SDT	7.3	6.6	5.7	5.8	6.3	5.2	4.6	33	1.66	−1.1	ND
2	C	CSII	5.5	5.4	5.4	5.1	5.0	5.0	5.1	34	2.60	0.5	ND
3	C	CSII	6.0	6.0	6.4	6.9	4.1	6.0	8.6	36	3.88	1.9	ND
4	C	CSII	8.0	6.7	6.4	5.8	8.8	8.4	7.1	36	3.35	1.0	3.4
5	D	SDT	5.3	7.3	7.6	5.2	8.1	6.3	6.3	37	3.82	1.4	5.2
6	C	CSII	7.8	6.2	6.5	6.2	7.1	8.2	6.2	38	3.90	1.3	3.1
7	C	SDT	5.5	5.0	5.3	4.6	4.4	4.3	5.0	38	3.27	0.0	4.0
8	C	CSII	6.0	5.8	5.9	5.3	8.0	7.4	5.6	38	3.43	0.4	4.3
9	B	CSII	5.5	5.3	5.1	5.2	4.1	4.5	4.3	38	3.02	−0.5	4.0
10	B	SDT	4.8	5.4	5.3	5.5	5.9	5.7	4.9	39	2.17	−2.5	4.1
11	D	CSII	6.6	6.5	6.9	6.8	5.6	8.2	4.6	39	3.57	0.3	3.8
12	B	CSII	7.2	6.0	5.7	4.9	5.9	6.0	5.9	39	3.68	0.6	3.2
13	B	SDT	5.6	5.6	5.5	5.2	5.5	6.0	6.8	40	4.77	2.8	ND
14	C	SDT	5.7	5.6	5.6	5.2	6.0	6.0	5.8	40	3.18	−0.7	4.2
15	C	CSII	6.6	5.9	6.0	6.4	6.0	6.5	5.9	40	3.25	−0.6	4.2
Mean ± SD			6.2 ± 0.9	6.0 ± 0.6	6.0 ± 0.7	5.6 ± 0.7	6.1 ± 1.4	6.2 ± 1.3	5.8 ± 1.1				

* SDT, split-dose therapy; CSII, continuous s.c. insulin infusion; ND, not determined.

remaining six were delivered vaginally. All infants were singletons. None of the infants suffered from neonatal asphyxia or had congenital abnormalities.

Measurements in mothers. Capillary blood glucose levels were determined with a reflectance meter (Boehringer Mannheim GmbH, Mannheim, Germany) used by the patients at home. The GsHb levels were determined in nondialyzed samples using the colorimetric method reported by Flückiger and Winterhalter (10).

Measurements in infants. All infants were delivered at the University Hospital of Groningen, and studied on the first day of life. Before and during the study, the infants did not receive any oral feeding. Infants were nursed in incubators at their thermoneutral temperature. The study was approved by the ethical committee of the University Hospital and Medical Faculty. All infants were studied after parental consent.

Glucose infusion was started within 1 h of birth in all infants. The GIR was randomly chosen and effectively ranged from 2.7 to 5.2 mg/kg/min. The Ra in the blood compartment was determined, using 6,6-[$^2H_2$]glucose, according to the procedures described by Bier *et al.* (11) and the prime dose constant rate infusion technique as described by Steele *et al.* (12). 6,6-[$^2H_2$] glucose 99 MPE was obtained from Merck Sharp and Dohme, Inc. (Dorval. Quebec, Canada). The tracer was tested for pyrogens. A weighed amount of the tracer was dissolved in sterile isotonic saline, and sterilized by passage through a 0.22-μm Millipore filter. The tracer was infused via a three-way connector together with the glucose maintenance infusion into a peripheral vein. After a prime dose of 5 mg/kg body weight in 10 min, the tracer was infused at a constant rate of 54 μg/kg/min with a syringe infusion pump (IVAC 700, IVAC Inc., San Diego, CA or Terfusion STC 521, Terumo Inc., Tokyo, Japan). Sixty min after the start of the constant rate infusion, blood samples were taken at half-hour intervals for 2 h for the determination of the blood glucose concentration and the measurement of 6,6-[$^2H_2$] glucose isotopic enrichment in plasma. Blood for determination of tracer enrichment was collected in sodium fluoride cups and centrifuged immediately; the plasma was kept at −20°C until analysis.

Aliquots of plasma (50 μL) were deproteinized with methanol and centrifuged, and supernatants were extracted with hexane to remove fatty acids. The water-methanol layer was collected and evaporated to dryness under N_2 at 40°C. Butane boronic acid in pyridine was added to the residue and derivatives were formed by heating for 30 min at 95°C (13). After cooling to room temperature, acetic anhydride was added to form the acetate. Finally, the derivative was dissolved in hexane and washed with 0.1 N HCl. Standards containing 0, 1, 2, 3, 4, and 5 MPE of 6,6-[$^2H_2$]glucose were prepared by mixing weighed aliquots of stable isotopically labeled glucose that were administered to the patient with weighed amounts of unlabeled glucose. On each day samples were analyzed, a calibration curve was constructed by plotting measured ion current ratios *versus* known MPE. Linear regression analysis was used to calculate slope and intercept values.

The isotopic enrichment of 6,6-[$^2H_2$]glucose was determined with an HP 5995 B gas chromatograph–mass spectrometer combination connected to an HP 9825B desktop computer (Hewlett-Packard Co., Palo Alto, CA). Selective ion monitoring was carried out at 70 eV. The dibutyl borate acetate derivatives were monitored at m/z = 297 $(M-57)^+$ for nonlabeled glucose and at m/z = 299 for labeled glucose.

At steady state, Ra was calculated using the following equation:

$$Ra = \frac{MPE\ inf}{MPE\ plasma} - 1 \times I$$

where MPE inf is the MPE of 6,6-[$^2H_2$]glucose in the infusate, MPE plasma is the MPE of 6,6-[$^2H_2$]glucose in plasma, and I is the rate of infusion of 6,6-[$^2H_2$]glucose.

The MPE plasma is the mean of the enrichments in plasma at the various time points during the constant-rate infusion period. Steady state was considered to be achieved when the concentrations of labeled and unlabeled glucose were approximately constant, with a coefficient of variation for the mean concentrations of less than 10%. For all measurements, the mean MPE in plasma was 1.06 ± 0.25%.

At steady state, GPR was calculated by subtracting the GIR from the appearance rate. The rate of disappearance of glucose from the glucose pool was assumed to be equal to Ra during steady state.

Venous blood glucose concentrations were determined using a glucose analyzer based on the glucose oxidase method (Yellow Springs, Inc., Yellow Springs, OH).

Blood samples for the determination of 3OHB, FFA, glucagon, and total insulin concentration were taken 1 h after the beginning of the study. Plasma 3OHB levels were measured by spectrophotometry using the enzymatic method described by Williamson

and Mellanby (14, 15). FFA concentrations in plasma were determined enzymatically with a commercial kit (NEFAC, Wako Chemicals GmbH, Neuss, Germany). Total plasma insulin levels in serum were measured by RIA using a Pharmacia kit (Pharmacia Diagnostics AB, Uppsala, Sweden). Glucagon was measured with the RIA kit for pancreatic glucagon from Novo Industri A/S (Copenhagen, Denmark). To increase the sensitivity to 5 ng/L, 0.5 mL of plasma was used instead of 0.1 mL.

Statistics. Correlations between the parameters of glucose kinetics, substrate concentrations, and postnatal age, and the glucose infusion rate were analyzed by applying linear regression models, using the SYSTAT software package (SYSTAT, Inc., Evanston, IL) on a personal computer.

RESULTS

Characteristics of mothers and infants. The mean GsHb level of each trimester and the GsHb level at delivery, together with the mean trimester blood glucose concentrations, are listed in Table 1. All women had GsHb concentrations at delivery within the normal range. The GsHb concentrations of pregnant nondiabetic women in our hospital range from 4.5 to 7.1% (16). Random blood glucose concentrations during pregnancy in these nondiabetic women ranged from 2.9 to 6.1 mmol/L.

Gestational ages, birth weights, SD scores of birth weight (or z score), and the neonatal GsHb levels are listed in Table 1. Mean blood glucose concentrations during the study and the postnatal age at the beginning of the study are shown in Table 2.

Neonatal glucose kinetics. The GIR, Ra of glucose into the glucose pool, and the GPR in individual infants are listed in Table 2. Also listed in this table are the mean FFA and the mean 3OHB concentrations in plasma during the stable isotope studies.

Plasma insulin concentrations were determined in nine infants, and ranged from 11.0 to 27.6 pg/L. Plasma glucagon levels were determined in 12 infants, and ranged from 11 to 74 ng/L.

STATISTICAL ANALYSIS

Data of mother-infant pairs. In this group of mother-infant pairs, the SD scores of birth weight of the infants were significantly correlated with the mean 3rd-trimester blood glucose concentrations (Fig. 1). Such a relationship was not observed with the mean 3rd-trimester GsHb concentrations or the GsHb concentrations at birth.

Neonatal glucose kinetics. In this study, no correlations were found between the neonatal GPR and the gestational age, birth weight, SD score of birth weight, glucose concentration, or hormone concentration. The GPR was correlated with postnatal age (Fig. 2) and with GIR. Therefore, a more detailed analysis of these relationships was done by multiple linear regression. The correlation of GPR with postnatal age, when corrected for GIR, remained highly significant ($p < 0.01$), whereas the correlation with GIR, when corrected for postnatal age, became insignificant ($p > 0.25$). Therefore, the postnatal age appeared to be a major determinant of the GPR.

Plasma FFA concentrations were not related to postnatal age, glucose concentration, or GIR. Plasma 3OHB concentrations were significantly related to postnatal age (Fig. 3). No relationships could be discerned between plasma 3OHB concentrations and plasma glucose concentrations or GIR.

Because the postnatal age appeared to be a major determinant for both GPR and the plasma 3OHB concentrations, we have analyzed the relationship between GPR and 3OHB concentrations. In Figure 4, this relationship is shown.

Glucose kinetics and regulation of diabetes during pregnancy. In this group of diabetic mother-infant pairs, we did not find any relationship between the neonatal GPR and the mean trimester GsHb concentration or mean trimester blood glucose concentration of the 1st, 2nd, or 3rd trimester.

DISCUSSION

This study describes control of insulin-dependent diabetes mellitus during pregnancy and subsequent neonatal glucose kinetics in 15 mother-infant pairs. Mothers were studied from the beginning of pregnancy till birth of their infants. The 24-h blood glucose profiles were used to adjust the dose of insulin. To assess control of glucose metabolism of the diabetic women, we used blood GsHb concentrations and 24-h blood glucose profiles taken at regular intervals throughout pregnancy, because both parameters reflect the mean blood glucose levels differently, *e.g.* GsHb changes slowly and is lowered in case of increased erythropoiesis (17). We calculated mean trimester values of both blood glucose concentration and GsHb. Because the majority of the values of the mean trimester blood glucose and GsHb level per patient were within the normal ranges, diabetes was considered tightly controlled in every patient.

Despite tight control, we did find a significant positive correlation between mean blood glucose concentrations during the last trimester of pregnancy and the SD scores of birth weight. This phenomenon has been well recognized in previous studies. In those studies, however, the diabetes was less strictly regulated, according to the blood glucose concentrations given (3, 18, 19). Our finding that the mean 3rd-trimester blood glucose concentrations were related to the SD scores of birth weight is in line with the Pedersen hypothesis (18). Because no relationship was

Table 2. *Postnatal age, GIR, Ra, GPR, blood glucose concentration, and plasma levels of 3OHB and FFA of infants during study*

Infant	Postnatal age (h)	GIR (mg/kg/min)	Ra (mg/kg/min)	GPR (mg/kg/min)	Glucose level (mmol/L)	3OHB (mmol/L)	FFA (mmol/L)
1	12	3.87	3.87	0.00	2.0	0.28	0.11
2	10	2.94	4.71	1.77	2.5	0.13	0.10
3	3	3.03	4.68	1.65	3.0	0.17	0.18
4	9	4.08	4.81	0.73	5.0	0.40	0.26
5	5	3.05	5.55	2.50	3.0	0.13	0.27
6	9	3.80	3.80	0.00	2.9	0.13	ND*
7	4	3.12	6.60	3.48	3.9	0.02	0.11
8	4	3.41	8.19	4.78	2.5	0.12	0.10
9	16	2.81	4.07	1.26	2.5	0.28	0.45
10	5	3.09	5.48	2.39	2.9	0.07	0.55
11	5	2.85	5.45	2.60	3.2	0.14	0.30
12	10	2.99	5.32	2.33	2.8	0.19	0.62
13	14	4.24	5.09	0.85	3.2	0.22	ND
14	5	2.68	4.96	2.28	2.5	0.27	ND
15	14	5.12	5.76	0.56	2.5	0.27	0.06
Mean ± SD		3.4 ± 0.7	5.2 ± 1.1	1.8 ± 1.3		0.19 ± 0.10	0.26 ± 0.19

* ND, not determined.

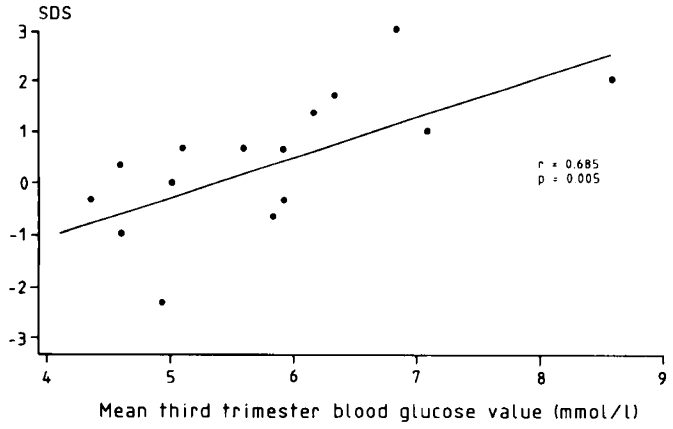

Fig. 1. SD score (*SDS*) of birth weight is significantly correlated with the mean 3rd-trimester blood glucose concentration in infants of mothers with tightly controlled diabetes, with 3rd trimester GsHb levels within the normal range.

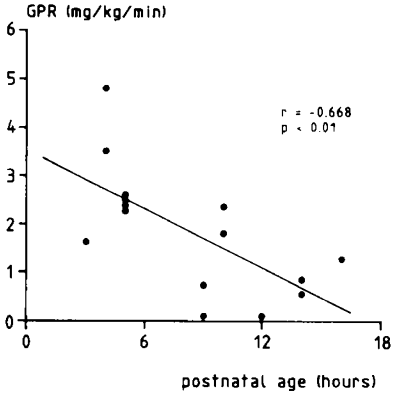

Fig. 2. Relationship between GPR and postnatal age, determined cross-sectionally in 15 infants of diabetic mothers.

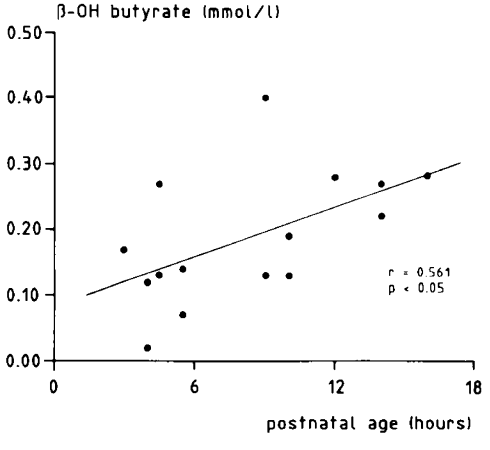

Fig. 3. In infants of mothers with tightly controlled diabetes, the 3OHB concentrations are significantly correlated with postnatal age.

observed between the neonatal insulin concentration in plasma and the SD score of birth weight, our finding does not fit in a more recently proposed concept, that the fetal hyperinsulinemia and subsequent fetal macrosomia are caused by transplacental transfer of insulin bound to antiinsulin antibodies, as proposed by Menon *et al.* (20) and Schwartz (21).

The regulation of neonatal glucose homeostasis is poorly developed directly after birth (22). In general, a period of readjustment is needed to allow this control to develop. Immediately after birth, newborn infants are in a catabolic state. Under such

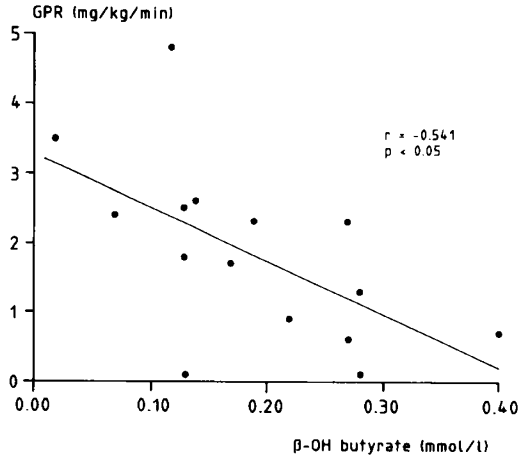

Fig. 4. The GPR is inversely correlated with the 3OHB concentration in infants of mothers with tightly controlled diabetes, indicating a qualitative normal postnatal metabolic adaptation.

conditions, glucose production diminishes and FFA and ketone bodies replace glucose as an energy source. Newborn infants of insulin-dependent diabetic mothers are prone to dysregulation of glucose homeostasis (4). From our data it appears that, at least in mothers with tightly controlled diabetes, control of glucose homeostasis is operative postnatally in their newborn infants. We observed with increasing postnatal age a decrease in glucose production and an increase in plasma ketone body concentration, such that both were inversely related (Fig. 4). The postnatal increase in ketone bodies in this study was comparable with previous reported data obtained in newborn infants born after pregnancies in healthy women (23, 24). In contrast to those studies, in this study a glucose infusion was used, as was regular clinical practice in these infants. Irrespective of this infusion, similar changes in energy metabolites were observed. Our data at high glucose infusion are consistent with the report of Lafeber *et al.* (25). They measured glucose production in infants at d 8, and the infants received an i.v. glucose infusion at a rate of 8 mg/kg/min. In these infants, no significant glucose production was observed.

Neonatal adaptation of glucose metabolism is regulated by hormones including catecholamines and pancreatic glucagon (26). In newborn infants, who are in a catabolic condition directly after birth, insulin does not seem to play a role in neonatal metabolic adaptation (27). Indeed, in this study we did not find a correlation between total plasma insulin concentrations and GPR in the nine infants in whom plasma insulin values were determined.

Plasma glucagon levels determined in 12 infants ranged from 11 to 74 ng/L. No correlation could be found between plasma glucagon levels and GPR or glucose disappearance rate. It appears that the plasma glucagon concentration itself does not reflect the extent of the stimulation of gluconeogenesis if individual infants are compared, as in this study. Even though we did not find a relationship between glucagon concentrations and parameters of glucose kinetics, glucagon may have played a role in glucose homeostasis in our infants, inasmuch as we found a clear correlation between postnatal age and GPR. The significance of the plasma glucagon levels measured in individual infants needs further exploration.

From this study, we conclude that postnatal glucose homeostasis of newborn infants of mothers with tightly controlled insulin-dependent diabetes mellitus appears to be normal. Our observation that the SD score of birth weight correlates positively with the mean last-trimester blood glucose level of the mothers may indicate that maternal diabetes still affects intrauterine growth, despite near-optimal insulin therapy.

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