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Postnatal Surge in Serum Calcitonin Concentrations: No Contribution to Neonatal Hypocalcemia in Infants of Diabetic Mothers

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ABSTRACT. It has been suggested that hypercalcitoninemia may contribute to neonatal hypocalcemia in infants of diabetic mothers (IDM). Because the role of calcitonin (CT) in Ca metabolism in humans is questionable, we hypothesized that serum CT peaks similarly after birth in IDM and controls and that serum Ca concentrations do not correlate with serum CT. Forty-seven term IDM (White classes B–RT) were compared with 31 controls. Controls were born after normal pregnancies, labors, and deliveries. Blood samples (cord and 24 h) were analyzed for Ca, Mg, parathyroid hormone (PTH), and CT. Repeated measures analysis showed increasing serum Mg, PTH, and CT, and decreasing Ca over time. The incidence of hypocalcemia was significantly higher in the diabetic group ($p < 0.01$) and the incidence of hypomagnesemia was borderline significantly higher ($p < 0.06$). There were no differences in cord or 24-h serum concentrations of CT between groups. In multiple regression analysis, serum Ca and PTH were correlated ($p < 0.02$, $R^2 = 0.33$), but not serum Ca and CT; the increase in serum PTH in relation to serum Ca at the nadir (24 h) correlated directly with serum Mg concentrations ($R^2 = 0.31$, $p < 0.05$). Thus, serum CT increases after birth irrespective of the rate of decrease of serum Ca in both IDM and controls; high CT concentrations observed after birth (as compared with adult norms) do not seem to play a role in the pathogenesis of neonatal hypocalcemia in IDM; and responsiveness of parathyroid gland at birth is adversely affected by hypomagnesemia, which supports the theory of functional hypoparathyroidism in Mg deficiency. (*Pediatr Res* 28: 493–495, 1990)

Abbreviations

IDM, infant of diabetic mother
CT, calcitonin
PTH, parathyroid hormone
NHC, neonatal hypocalcemia

IDM are at high risk for NHC, which may occur in up to 50% of these infants (1). Perinatal asphyxia and prematurity, well-known risk factors for NHC, also occur at high incidence in IDM (2, 3). However, it was shown in a prospective, matched-control study that NHC in IDM is significant even after controlling for the aforementioned variables (1). Leading theories related to the pathophysiology of NHC in IDM include: *1*) maternal-fetal Mg-deficient state, due to maternal glycosuria (4), leading to fetal hypoparathyroidism and subsequent NHC (1, 5) and *2*) neonatal hypercalcitoninemia (6, 7). The latter theory is supported by evidence that the neonatal surge in serum CT concentrations found in normal neonates also occurs in IDM, which might seem inappropriate when one considers the concomitant decrease in serum Ca. Studies supporting this theory were limited by small sample size, with only one showing an inverse correlation between serum Ca and CT concentrations in 11 IDM (6). We conducted this prospective study to determine whether CT plays any role in NHC in IDM when simultaneous measurements of serum Mg and PTH concentrations are taken into account.

MATERIALS AND METHODS

Patients. Since 1979, 47 full-term (37–41 wk gestation) infants of insulin-dependent diabetic mothers (White classes B–RT) (8) were prospectively studied as part of an NIH-funded program project grant, "Diabetes in Pregnancy." Preterm infants were excluded from this study because of the confounding influences of gestational age on neonatal calcium metabolism (1). The 47 IDM were compared with a group of 31 term infants of nondiabetic pregnant women [normal glucose challenge test at 28 wk gestation (9)] born after uncomplicated pregnancies, labors, and deliveries. This study was approved by the Review Board on Investigations Involving Human Beings of the University of Cincinnati Medical Center Hospital. Written informed consent was obtained from one of the legal guardians of each infant before enrollment into the study.

The aims of glycemic control in diabetic pregnancy were a preprandial blood glucose concentration below 5.55 mmol/L (100 mg/dL) and a 90-min postprandial blood glucose concentration below 7.71 mmol/L (140 mg/dL). Pregnant patients were hospitalized when necessary to maintain these goals of glycemic control. Maternal blood glycosylated Hb A_1 contents were measured every 4 wk to determine if adequate glycemic control was achieved. Pre- or postprandial capillary glucose concentration was alternatively measured at each weekly visit. In each patient, pre- or postprandial blood glucose values were averaged over each trimester as mean pre- or postprandial blood glucose concentrations per trimester (10).

Data collection. Diabetes was categorized using the White classification (8). Blood samples were collected from infants in both groups at birth from a double-clamped segment of umbilical cord and at 24 h of life for determination of Ca, Mg, PTH, and CT. Gestational age was calculated from the last menstrual period and confirmed within ±2 wk of Ballard score (10). We defined NHC, using the traditional definition supported by the data

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collected in our own laboratories (11) as a 24-h serum Ca concentration below 8 mg/dL and neonatal hypomagnesemia as a 24-h serum Mg concentration below 1.6 mg/dL (12). Serum glucose was measured in all infants at 2 h of age.

Biochemical analyses. Serum Ca and Mg concentrations were measured by atomic absorption spectrophotometry (13). The normal pediatric range for Ca in our laboratory is 2.15 to 2.72 mmol/L (8.6 to 10.9 mg/dL), with an interassay coefficient of variation of 1.2%. The normal pediatric range for Mg is 0.70 to 1.02 mmol/L (1.7 to 2.5 mg/dL) with an interassay coefficient of variation of 2.8%. Serum PTH assay was performed by a modification of the RIA of Arnaud *et al.* (14) using an antiserum raised in guinea pig. The antibody recognizes the entire 1-84 molecule (15). The serum standard was obtained from a hyperparathyroid subject. The normal adult range, calculated using the maximum likelihood method (16), which statistically accounts for undetectable values, is 33 to 117 μLEq/mL in nonpregnant adults in our laboratory. The interassay coefficient of variation is 14%. Serum CT concentration was measured by a modification of the RIA procedure described by Heath and Sizemore (17). Normal adult values are less than 107 pg/mL, with intraassay and interassay coefficients of variation of 6 and 15%, respectively. Pre- and postprandial capillary blood glucose concentrations were measured with a reflectance meter (Ames dextrometer, Ames Co., Elkhart, IN) that was calibrated weekly and the accuracy of which was verified every 4 wk with simultaneous sample measured in the University Hospital Clinical Chemistry Laboratory. Total blood glycosylated Hb was measured by Isolab column chromatography with an interassay coefficient of variation of 7.2% and a normal range of 5.5 to 8.5% (18).

Data analysis. Data were analyzed using the Statistical Analysis System (SAS Institute, Inc., Cary, NC). Continuous data were tested for normality and were analyzed using analysis of variance techniques and *t* test for normal data and Wilcoxon test for nonnormally distributed data. Fisher's exact test was used for analyzing categorical variables. Multiple regression analysis was used to determine the relationship between neonatal serum Ca concentrations and serum Mg, PTH, and CT concentrations. Analysis of covariance was used to detect differences between the diabetic and nondiabetic groups with respect to these relationships. Linear regression was used to test a relationship between serum Mg concentrations and serum PTH or the ratio of the PTH surge over the Ca nadir (delta PTH/Ca). Delta PTH/Ca is defined as [PTH (24 h)] − PTH (cord)/Ca (24 h). The delta PTH/Ca ratio has been previously used to relate the PTH response to the lowest serum Ca concentration (1, 5). Data are expressed as mean ± SEM; a p value of less than 0.05 was considered significant.

RESULTS

The demographic characteristics of the population studied (in terms of maternal age, age at diagnosis of maternal diabetes, White classification, gestational age, birth weight, and Apgar scores) are shown in Table 1. Indices of glycemic control in pregnancy are shown in Table 2.

Due to standard policy of delivery of IDM soon after 37 wk of gestation (term), these infants had a lower mean gestational age than control infants. Analysis of covariance, adjusting for this difference, revealed that, within the narrow gestational age range considered, the length of gestation had no significant impact on the biochemical and hormonal variables studied. Also, birth weight, which was significantly higher in IDM, was not a significant variable in covariance analysis.

Table 1. *Demographic characteristics of study population**

	IDM (n = 47)	Controls (n = 31)	Significance
Gestational age (wk)	38.1 ± 0.2	39.8 ± 0.2	$p < 0.01$
Birth wt (kg)	3.6 ± 0.69	3.3 ± 0.07	$p < 0.01$
White class B	6 (12.8)	NA†	
White class C	18 (38.3)	NA†	
White class D-RT	23 (48.9)	NA†	

* Data expressed as mean ± SEM or n (%).
† Not applicable.

Table 2. *Indices of glycemic control in diabetic pregnancies**

	Trimester 1	Trimester 2	Trimester 3
Mean preprandial blood glucose concentration (mg/dL)	125 ± 7	113 ± 5	122 ± 5
Mean postprandial blood glucose concentration (mg/dL)	183 ± 8	151 ± 7	162 ± 9
Glycohemoglobin A_1 content (%)†	10.1 ± 0.3	8.2 ± 0.2	7.8 ± 0.2

* Data are expressed as mean ± SEM.
† Sampling time at 19 wk, 26 wk, and at delivery, representing glycemic control during the 1st, 2nd, and 3rd trimesters, respectively.

Table 3. *Mean ± SD serum Ca, Mg, PTH, and CT in IDM and controls*

	IDM (n = 47)	Controls (n = 31)	Significance*
Ca (mg/dL)			
Cord	10.3 ± 1.1	10.2 ± 0.5	NS
24 h	8.6 ± 0.9	9.0 ± 0.6	NS
Significance†	<0.01	<0.01	
Mg (mg/dL)			
Cord	1.77 ± 0.26	1.82 ± 0.21	NS
24 h	1.87 ± 0.28	1.91 ± 0.16	NS
Significance†	<0.05	<0.05	
PTH (μLEq/mL)			
Cord	25 ± 15	35.9 ± 22	NS
24 h	50.5 ± 37.2	50.5 ± 23	NS
Significance†	<0.01	<0.01	
CT (ng/mL)			
Cord	42 ± 37	58 ± 90	NS
24 h	228 ± 136	220 ± 130	NS
Significance†	<0.01	<0.01	

* IDM compared with control.
† Cord blood compared with 24-h values.

Table 3 shows the mean serum Ca, Mg, PTH and CT concentrations in IDM and controls. Repeated measures analysis of variance showed significant differences in both groups over time (decreasing serum Ca, increasing serum Mg, PTH, and CT concentrations). Mean serum Ca, Mg, PTH, and CT did not significantly differ between groups at any time point. However, the incidence of neonatal hypocalcemia (serum Ca at 24 h < 2.0 mmol/L, or 8 mg/dL) was significantly higher in IDM (30%) than in controls (3.2%) ($p = 0.003$) and the incidence of neonatal hypomagnesemia (serum Mg at 24 h < 0.66 mmol/L, or 1.6 mg/dL) was borderline significantly higher in IDM (10.6%) than in controls (0.0%) ($p = 0.06$).

We performed a multiple regression analysis in which all patients (IDM and controls) were included; serum Ca at 24 h (nadir) was the dependent variable, with serum Mg, PTH, and CT used as independent variables. This analysis showed that serum Ca correlated significantly only with serum PTH ($R^2 = 0.33$, $p < 0.02$). The extent of the postnatal PTH surge in relation to serum Ca at 24 h (Δ PTH/Ca) correlated significantly with serum Mg concentration at 24 h ($R^2 = 0.31$, $p < 0.05$). There was no correlation between the nadir serum Ca and the lowest serum glucose concentration in the IDM group.

DISCUSSION

The exact physiologic role of CT in the perinatal period—or in any other period in life—is still poorly understood (19).

Calcitonin has hypocalcemic effects by its combined action on bone and kidney. However, patients with medullary carcinoma of the thyroid may have considerable elevations of serum CT concentrations without detectable hypocalcemia (19). Furthermore, patients with thyroid dysgenesis, although having abnormal calcemic curves when submitted to a calcium load, do not have significant baseline elevation of serum Ca (20). There is no disease state due to isolated CT deficiency, although it has been recently suggested that such deficiency might lead to hypercalcemia in Williams syndrome (21). A surge in serum CT concentrations occurs at birth, despite the decreasing serum Ca concentrations that follow cord clamping and interruption of transplacental Ca transport. The serum CT values reached with this surge are higher than at any other period in life (22). The significance and potential physiologic role in this apparently paradoxical CT surge are unknown. Also, Klein *et al.* (23) observed that postnatal CT concentration from birth to 6 y of age paralleled the age-related decline in rate of bone growth. They speculated that CT may play a role in bone growth or mineralization.

In our study, irrespective of the extent of decrease in serum Ca, serum CT concentrations increased to very similar values in both groups and serum Ca concentrations did not correlate with serum CT concentrations. Bergman *et al.* (6) speculated that neonatal hypoglycemia in IDM might lead to increased glucagon secretion, and because glucagon is known to both lower serum Ca (24) and stimulate CT secretion (6), it might, theoretically, directly and indirectly cause neonatal hypocalcemia. A recent study from our group demonstrated that, in asphyxiated infants, there is an increased serum CT concentration (presumably stress-induced) and that postnatal serum Ca concentrations correlate inversely with serum CT concentrations (25). However, in the same study, serum CT did not correlate with serum glucagon. Furthermore, the glucagon response to hypoglycemia appears to be blunted in IDM because hypoglycemic and normoglycemic IDM have similar serum glucagon concentrations (26). There is a lower serum glucagon concentration in IDM compared with controls (27).

The PTH response to decreasing serum concentrations, assessed by the ratio Δ PTH/Ca, correlated with serum Mg concentrations. This would support the theory of Mg deficiency as a cause of functional hypoparathyroidism in newborn infants (28). However, hypoparathyroidism might not be the only explanation for NHC in IDM. Because a relative resistance to PTH in Mg deficiency has also been documented in adults, in theory, resistance to PTH might also be involved (29).

We conclude that serum CT concentrations increase at birth in IDM and controls, irrespective of the degree of hypocalcemia. CT does not appear to play a significant role in the pathophysiology of NHC in IDM. However, our diabetic patients were particularly well controlled, in that their glycohemoglobin concentrations were within the normal range as early as the 2nd trimester of pregnancy. Thus, one should raise the possibility that our conclusions may not hold in a poorly controlled group of diabetic patients.

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