Rapid Publications

High Plasma Norepinephrine Concentrations at Birth in Infants of Diabetic Mothers

JAMES B. YOUNG, WAYNE R. COHEN, ELIZABETH B. RAPPAPORT, AND LEWIS LANDSBERG

SUMMARY

Analysis of plasma norepinephrine (NE) concentrations in umbilical artery and vein from infants of diabetic and nondiabetic mothers revealed high plasma NE values in those of diabetic mothers. While birth weight and arterial plasma NE did not correlate in infants of nondiabetic mothers ($r = 0.07$, NS), birth weight and plasma NE were related inversely in infants of diabetic mothers ($r = -0.73$, $P < 0.05$). DIABETES *28*:697–699, July 1979.

Although considerable improvement in management of diabetic pregnancy has occurred over the past decade, infants of diabetic mothers (IDM) remain at greater risk of perinatal complications than those of nondiabetic mothers (control infants).[1,2] The underlying pathophysiologic mechanisms responsible for this excess morbidity and mortality are unclear. Because the sympathoadrenal system is needed to regulate the circulation and metabolism, changes in the functional state of the developing sympathetic nerves and/or adrenal medulla might contribute to altered physiology in IDM. The following study was undertaken to assess sympathoadrenal activity in IDM.

EXPERIMENTAL PROCEDURE

Samples of cord arterial and venous blood from the placentas of infants of nine diabetic and eight nondiabetic mothers were collected into iced, heparinized tubes immediately on delivery and after section of the cord. Perchloric acid extracts of plasma were frozen at −20 °C until analyzed for norepinephrine (NE), usually in 1 wk. Plasma NE was determined by radioenzymatic assay.[3]

No attempt was made to influence prenatal or intrapartum management of the diabetic patients. As is customary at this institution, urinary estriol measurements and antepartum fetal heart rate monitoring were taken on all pregnant diabetic women during the third trimester. No diabetic pregnancy was terminated on account of suspected fetal compromise. All 17 deliveries in diabetic and nondiabetic women were uneventful clinically; two patients (one diabetic and one nondiabetic) were excluded from analysis because of clinically evident hypoxia secondary to complications of anesthesia in one and to difficulties in delivery of the infant by cesarean section in the other. Clinical data from mothers and infants were gathered by chart review. The study was approved by the Committee on Clinical Investigation of the Beth Israel Hospital. Data are presented as means ± SEM. Statistical analysis employed Student's *t* test for unpaired variables, chi-square test, and coefficient of correlation.[4]

RESULTS

In IDM, plasma NE concentrations in umbilical artery and vein were significantly higher than in infants of nondiabetic mothers (Table 1). Cord artery NE concentrations in our study were similar to those of investigators who used a different radioenzymatic assay[5] but lower than those obtained by fluorometric methodology.[6] Arterial concentrations of NE in all cases exceeded venous levels, as was noted before in normal infants,[5,6] indicating that the fetus is the principal source of circulating NE in fetal blood. Since the ratios of arterial:venous NE in cord plasma were similar in the two groups, it is unlikely that decreased placental clearance of NE accounts for the high NE concentrations in IDM.

Clinical information about the mothers and their infants is shown in Table 2. The women were about the same age, had a similar exposure to anesthesia, and had a similar incidence of vaginal delivery and cesarean section.

From the Departments of Medicine and Obstetrics-Gynecology and the Thorndike Laboratory, Harvard Medical School and Beth Israel Hospital, Boston, Massachusetts.

Reprint requests should be addressed to Dr. James B. Young, Department of Medicine, Beth Israel Hospital, 330 Brookline Avenue, Boston, Massachusetts 02215.

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TABLE 1
Plasma NE at birth in infants of nondiabetic mothers (controls) and infants of diabetic mothers (IDM)

Cord plasma NE (ng/ml)	Controls	IDM	P
Artery	1.73 ± 0.22	5.27 ± 1.50	<0.05
Vein	0.32 ± 0.10	0.83 ± 0.19	<0.05
A/V ratio	8.5 ± 2.1	8.4 ± 2.9	NS

Parturition occurred earlier in the diabetic women (at 37.7 ± 0.4 wk of gestation) than in nondiabetic women (at 39.4 ± 0.6 wk), consistent with current obstetric practice. Although mean birth weights were similar in the two groups, the range was greater in the diabetic women (2448–4763 g) than in the control women (2608–3817 g). The sex ratio of the infants was the same in both groups. Apgar scores were markedly lower at 1 min in IDM than in control infants, but by 5 min the difference had disappeared. Arterial NE values did not correlate with 1-min Apgar scores in IDM ($r = -0.04$).

Arterial plasma NE levels in IDM increased with the mother's diabetes class: mean plasma NE concentration in White class A diabetic women was 1.74 ng/ml ($n = 2$); in class B, including insulin-requiring gestational diabetic women, arterial NE was 4.37 ng/ml ($n = 4$); and in class C, NE was 8.81 ng/ml ($n = 3$). Although no correlation between arterial plasma NE concentration and birth weight was observed in infants of nondiabetic women ($r = 0.07$), birth weight and plasma NE were inversely related in IDM ($r = -0.73$, $P < 0.05$) (Figure 1). No correlation was demonstrable between gestational age and plasma NE in either IDM or control infants, and the relationship between plasma NE and birth weight in IDM was still apparent when birth weight was expressed as percentile for gestational age to allow correction for the slight difference in gestational age between IDM and control.

DISCUSSION

The factor(s) responsible for the increased arterial plasma NE concentration in IDM described in this report is (are) currently unknown. Parturition, itself, increases plasma NE levels in sheep[7] and human fetuses.[5] While this may account, in part, for the high plasma concentrations in these infants compared with normal adult levels of 0.2–0.3 ng/ml,[3] such a sympathoadrenal stimulus does not explain the NE elevation in IDM. Mode of delivery, likewise, cannot account for the observed difference since the incidence of vaginal delivery and cesarean section was the same in both groups. Furthermore, previous investigators reported no difference between cord arterial plasma NE concentrations during uneventful deliveries by the two methods.[5,6]

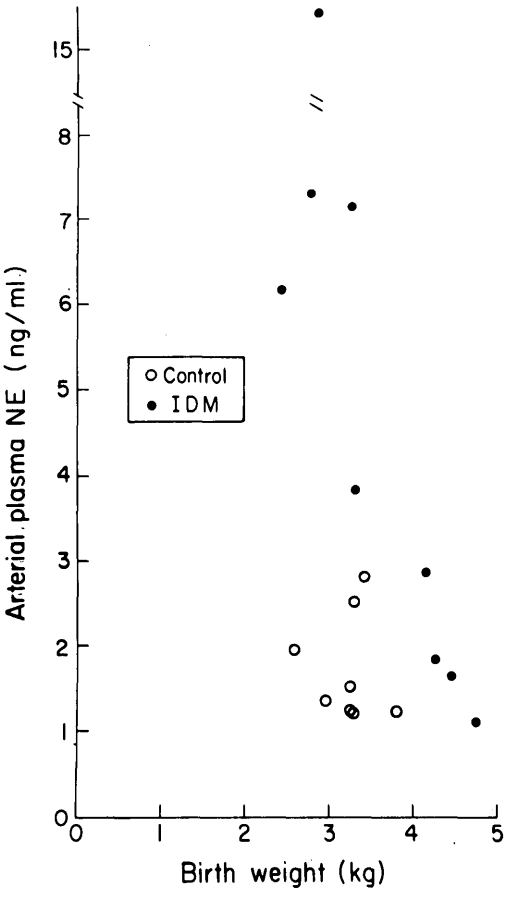
Abnormal glucose concentrations could contribute to the high NE value in IDM. Hypoglycemia elevates plasma NE by stimulating adrenal medullary secretion, but since IDM had access, until moments before sampling, to maternal glucose and maternal hypoglycemia was not observed before or during delivery, this explanation seems unlikely. Hyperglycemia (above 150 mg/dl) in fetal sheep was reported to increase fetal lactate values and decrease pH by unknown mechanisms.[8] Since acidosis stimulates sympathoadrenal activity, hyperglycemic acidosis in IDM could have led to the elevation in plasma NE. Previous studies, however, showed little difference in cord plasma glucose concentrations between infants of diabetic and those of nondiabetic mothers because of the apparently intact insulin secretory apparatus in IDM,[9,10] reducing the attractiveness of that hypothesis.

A possible contributing factor is fetal hypoxia. Elevated plasma catecholamines were measured in infants who develop hypoxia during parturition.[6] In the two infants

TABLE 2
Clinical data on mothers and infants

	Controls	Diabetics	P
Maternal age (yr)	28.9 ± 2.0	30.6 ± 1.7	NS
Anesthesia (general/regional/none)	3/4/1	2/7/0	NS
Mode of delivery (vaginal/cesarean)	2/6	1/8	NS
Age of infant at birth (wk)	39.4 ± 0.6	37.7 ± 0.4	<0.05
Birth weight (g)	3247 ± 123	3603 ± 278	NS
Infant's sex (M/F)	5/3	5/4	NS
Apgar scores			
1 min	8.6 ± 0.2	6.7 ± 0.6	<0.02
5 min	9.6 ± 0.2	9.1 ± 0.3	NS

FIGURE 1. Relationship between cord artery plasma norepinephrine (NE) concentration and birth weight in infants of diabetic (IDM) and nondiabetic (control) mothers. Coefficient of correlation between plasma NE and birth weight in control infants was 0.07 (NS) and in IDM was −0.73 ($P < 0.05$).



excluded from this study on the basis of clinical hypoxia secondary to complications of delivery, arterial plasma NE concentrations were markedly elevated (35.3 ng/ml in the IDM and 42.1 ng/ml in the control infant). Although in the earlier report the hypoxic infants usually exhibited abnormal fetal heart rate patterns[6] and in this series they were normal, undetected reductions in fetal oxygenation during delivery could conceivably have led to sympathoadrenal stimulation and, in some IDM, to depression of 1-min Apgar scores. The lack of correlation between plasma arterial NE and Apgar scores at 1 min does not support the concept that lower 1-min Apgar scores in IDM reflect fetal hypoxia. In one infant, for example, a plasma arterial NE value of 1.85 ng/ml accompanied a 1-min Apgar score of 3, associated with evidence of meconium aspiration. Chronic, impaired oxygen delivery probably was not responsible for the high NE values in IDM, since Apgar scores in IDM at 5 min were normal. For hypoxic stimulation of the sympathoadrenal system to be related to birth weight in IDM, smaller IDM must, in some way, be more susceptible to the development of hypoxia during delivery or respond more vigorously than the larger infants to existing hypoxia.

An alternative, and not mutually exclusive, hypothesis derives from recent work demonstrating an increase in sympathoadrenal activity with feeding.[11] The intact insulin secreted in IDM[9,10] and the hypothesis that insulin serves as an important link between nutrient ingestion and sympathoadrenal activity[12] suggest that the IDM exposed in utero to excessive quantities of glucose and other nutrients might be subject to chronic sympathoadrenal stimulation. Increased sympathoadrenal activity might then oppose weight gain, leading to the observed relationship between plasma NE and birth weight. Whether dietary stimulation of sympathoadrenal activity occurs in human fetuses and whether such an influence can account for the high plasma NE concentrations in IDM are unknown, but they warrant further study.

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