Deficient Counterregulation: A Possible Risk Factor for Excessive Fetal Growth in IDDM Pregnancies

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OBJECTIVE — The rate of macrosomia in infants born to women with IDDM remains high despite intensive insulin therapy and good glycemic control. We hypothesized that one of the factors contributing to this high rate of macrosomia is deficient counterregulatory hormonal responses to hypoglycemia.

RESEARCH DESIGN AND METHODS — Hypoglycemia was induced in 17 women with IDDM and 10 normal control subjects at 24–28 and at 32–34 weeks' gestation, using the hypoglycemic clamp technique. Plasma glucose concentrations were decreased to 3.3 mmol/l and maintained at this level for 1 h. Blood samples were drawn every 15 min for measurement of counterregulatory hormone concentrations.

RESULTS — All 17 women with IDDM had diminished epinephrine responses to hypoglycemia, compared with control subjects. Eight of the women with IDDM (nonresponders) had minimal or no responses (<165 pmol/l above baseline) and nine women (responders) had a moderate response (244–764 pmol/l). Of the eight nonresponders, seven had large infants (birth weight in the upper quartile), while only three of the nine responders had large infants ($P < 0.05$).

CONCLUSIONS — Severely impaired counterregulatory epinephrine responses to hypoglycemia in pregnant women with IDDM may be a factor contributing to excessive fetal growth. We speculate that in these women, recurrent episodes of hypoglycemia may result in frequent bouts of increased caloric intake, with repeated episodes of transient hyperglycemia leading to fetal hyperinsulinism and excessive fetal growth.

Intensive insulin therapy has become a standard mode of treatment for pregnant women with IDDM. The goal of such therapy is to improve glycemic control, thereby improving pregnancy outcome by decreasing the rate of early pregnancy loss and major malformations as well as reducing the incidence of obstetric and neonatal complications (1,2). Improved glycemic control during pregnancy in women with diabetes reduces the rate of macrosomia (3). Nevertheless, women with IDDM continue to have an inordinately high rate of macrosomic infants despite intensive insulin therapy (4–6). We hypothesized that one possible factor contributing to excessive fetal growth in these pregnancies is deficient maternal counterregulatory responses to hypoglycemia.

RESEARCH DESIGN AND METHODS

The study was approved by the Institutional Review Board, and all participating subjects signed an informed consent statement.

Seventeen pregnant women with IDDM (study group) and 10 healthy pregnant women (control group) underwent hypoglycemic clamp studies to evaluate the counterregulatory hormonal responses to hypoglycemia during pregnancy. Each subject was studied twice during pregnancy, at 24–28 weeks' and at 32–34 weeks' gestation. Women in the study group were admitted to the Clinical Research Center on the evening before the study. The evening insulin dose (or doses) was omitted, and no caloric intake was allowed after dinner. Subjects remained supine throughout the night, and blood glucose concentrations were maintained at 4.4–5.5 mmol/l with a varying-rate infusion of regular insulin (150 units/500 ml 0.9% NaCl). On the morning of the study, all subjects underwent a hypoglycemic clamp study using the Miles Biostator (Elkhart, IN).

An 18-gauge double-lumen catheter was inserted into a vein in the left hand or forearm for continuous sampling by the Biostator. Additional blood samples were obtained from a different vein in the same arm, and solutions were infused by the Biostator into a vein in the contralateral arm. The left arm was placed in a heating device to arterialize venous blood samples. After an initial stabilizing period of 30 min, two baseline blood samples were drawn 15 min apart to determine baseline levels of counterregulatory hormones. Plasma glucose concentrations were lowered to 3.3 mmol/l, and this level of hypoglycemia was maintained for 1 h. Plasma glucose concentrations were determined every 5–15 min to verify Biostator glucose sensor accuracy using the YSI Model 2300 STAT (Yellow Springs Instruments, Yellow Springs, OH). Blood samples were drawn every 15 min and at 30 and 60 min after completion of the hypoglycemic phase. All samples were placed in ice and then separated and stored at −20°C for later analysis. Fetal heart rate and uterine activity were continuously monitored during all studies.

Management of pregnant women with diabetes has been described elsewhere (7). Briefly, women with IDDM were enrolled in the Diabetes in Pregnancy program before 9 weeks' gestation and managed with intensive insulin therapy throughout pregnancy. Goals of glycemic control were a preprandial blood glucose concentration <5.5 mmol/l and a 90-min postprandial concentration <7.8 mmol/l.

Birth weight centiles of infants were determined using locally developed growth curves that are specific for gestational age, sex, and race. For the purpose of this study,

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infants weighing in the upper quartile (above the 75th centile for gestational age) were defined as large infants.

Plasma epinephrine was extracted in 0.1 mol/l perchloric acid and measured by high-pressure liquid chromatography (electrochemical detection), using 100-µl samples (8). The limit of detection is 54.6 mmol/l, and inter- and intra-assay coefficient of variation is <10%. Plasma glucagon was measured by radioimmunoassay (9). Limit of detection is 12 ng/l, and the coefficient of variation for interassay is 12% and for intra-assay is 4%. Baseline hormonal concentrations for each subject were determined from the average of the two baseline values. The peak hormonal response for each subject was determined from the highest hormonal concentration during the 1-h hypoglycemia period minus the basal hormonal concentration. A mean peak response was determined for each subject from the results of the two studies at 24–28 and 32–34 weeks. Statistical analyses were performed using SAS (Statistical Analysis Systems, Cary, NC). The χ^2 test, Fisher's exact test, two-tailed Student's *t* test, and Spearman rank correlation were used as appropriate.

Table 1—*Characteristics of responders and nonresponders to hypoglycemia*

	Responders	Nonresponders	*P*
n	9	8	
Peak epinephrine (pmol/l)	284 ± 142	60 ± 33	0.003
Age (years)	24 ± 5.5	28.4 ± 3.7	NS
Disease duration (years)	15 ± 8.1	18.8 ± 4.3	NS
Microvascular disease	1 (11%)	3 (38%)	NS
Prepregnancy weight (lbs.)	132 ± 12	145 ± 17	NS
Pregnancy weight gain (lbs.)	35.1 ± 7.9	33.8 ± 13.3	NS
Gestation at delivery (weeks)	37.0 ± 3.2	37.5 ± 2.2	NS
Mean HbA_1 (%)			
1st trimester	8.5 ± 1.6	8.5 ± 1.6	NS
2nd trimester	6.5 ± 1.1	6.8 ± 0.7	NS
3rd trimester	6.8 ± 0.9	6.5 ± 0.5	NS
Mean preprandial glucose (mmol/l)			
1st trimester	6.8 ± 1.6	6.5 ± 1.0	NS
2nd trimester	6.7 ± 1.4	7.0 ± 0.9	NS
3rd trimester	6.4 ± 1.4	6.6 ± 1.2	NS
Mean birth weight (grams)	3,171 ± 862	3,559 ± 864	NS
Mean birth weight (centile)	53 ± 31%	79 ± 22%	0.08
Large infant (>75th%)	3 (33%)	7 (87.5%)	<0.05

Data are means ± SD or *n* (%). NS, not significant. Normal range of HbA_1 is 5.5–8.5%.

RESULTS — There were no significant demographic differences between women with diabetes and controls: age (mean ± SD) was 26.2 ± 4.7 and 28.2 ± 5.8 years; mean gravidity was 2.4 ± 1.3 and 2.5 ± 1.4; mean parity was 0.7 ± 0.6 and 1.0 ± 0.8; and 94 and 100% of subjects were white, respectively. Duration of disease (mean ± SD) in women with diabetes was 15.7 ± 7.1 years; HbA_1 concentrations in women with diabetes were 6.6 ± 0.87% at 24 weeks' and 6.7 ± 0.9% at 34 weeks' gestation (1.5 and 1.6 SD above the mean for nondiabetic subjects, respectively). Fetal heart rates were normal, and no abnormalities of uterine activity were observed during any of the studies.

Plasma glucose concentrations were lowered and maintained at 3.3 ± 0.1 mmol/l in a similar manner in both groups during both studies. Women with IDDM had significantly diminished peak epinephrine responses to hypoglycemia compared with control subjects [median (25%, 75%)], 224 (164, 311) pmol/l and 747 (502, 1,250) pmol/l, respectively ($P < 0.05$). Glucagon peak responses were diminished in both groups, at 15.2 (9.1, 22.6) and 22.2 (12.5, 30.2) ng/l, respectively.

In the study group of IDDM women, two subgroups were readily distinguished based on their epinephrine responses to hypoglycemia during pregnancy: one group of eight women ("nonresponders") had a negligible or no response to hypoglycemia, within 2 SD of the mean baseline concentration of epinephrine (<165 pmol/l), while the other group of nine women ("responders") had a noticeable, albeit diminished (compared with nondiabetics) epinephrine response to hypoglycemia (244–764 pmol/l). Characteristics of subjects in both groups are presented in Table 1. Although mean birth weights were similar in both groups, birth weight percentiles (adjusted by gestational age, race, and sex) were marginally greater in the nonresponders. Seven of the eight nonresponders had large infants (>75th centile for gestational age), while only three of the nine responders had large infants ($P < 0.05$ by Fisher's exact test).

Peak epinephrine responses were negatively correlated with maternal weight gain during pregnancy ($r = -0.39$, $P = 0.13$), the frequency of documented hypoglycemia below 2.2 mmol/l ($r = -0.26$, $P = 0.36$), and the frequency of severe symptomatic hypoglycemia in the second trimester requiring the assistance of another person ($r = -0.5$, $P = 0.06$). Weight gain was positively correlated with the frequency of severe symptomatic hypoglycemia ($r = 0.47$, $P = 0.09$).

CONCLUSIONS — Most patients with IDDM lose the ability to mount a glucagon counterregulatory response to hypoglycemia shortly after the onset of diabetes. The glucagon response to hypoglycemia is also diminished in healthy pregnant women (10) and in pregnant rats (11). In the absence of a glucagon response, successful counterregulation in pregnant women with IDDM is dependent solely on the ability to mount an effective epinephrine response when hypoglycemia occurs. However, many patients with long-standing IDDM also have diminished epinephrine responses to hypoglycemia (12), and these responses are further diminished during intensive insulin therapy (13) and during pregnancy (14). In the absence of an effective epinephrine counterregulatory response, hypoglycemia is likely to be recurrent, resulting in frequent variations in blood glucose concentrations.

Based on our data, we suggest that a diminished epinephrine response to hypoglycemia in pregnant women with IDDM is a risk factor for excessive fetal growth. In this study we used the 75th centile as a cutoff point for the definition of large infants to allow detection of subtle differences in fetal growth despite the small sample size. Although birth weights above the 75th centile do not meet the definition of macrosomia (>90th centile), we believe that the

difference between the two groups with respect to the weight distribution by gestational age has clinical relevance. We speculate that the diminished epinephrine response predisposes these women to recurrent episodes of hypoglycemia during pregnancy, which are alarming both to the patient and to the people around her, and may lead to recurrent episodes of exaggerated caloric intake in an effort to correct the hypoglycemic episodes. These recurrent episodes of hypoglycemia and subsequent increased caloric intake may result in corresponding fluctuations in fetal blood glucose that may predispose the fetus to hyperinsulinism and excessive growth. Exposure of the fetal pancreas to glucose in excess of basal levels can induce precocious maturation and hyperplasia of the fetal β-cells (15). Indeed, maternal glucose intolerance appears to increase fetal insulin output as early as 16–20 weeks' gestation (16). These data suggest that the fetus may already be prone to develop hyperinsulinism during the first half of pregnancy, which is the time when most hypoglycemic episodes occur (17).

Although it may be argued that women with intact counterregulatory responses would be more inclined to respond to symptomatic hypoglycemia with increased caloric intake, our data do not support that premise. Our data suggest that pregnancy weight gain may be negatively correlated with peak epinephrine response to hypoglycemia, supporting our hypothesis that the patients with the most deficient counterregulatory responses are those who have more frequent neuroglycopenic episodes and respond with increased caloric intake. Apparently, the resulting fluctuations in blood glucose concentrations do not change the overall average glucose or glycohemoglobin concentrations and are not well documented by the patients.

Good glycemic control during pregnancy in women with diabetes is undoubtedly the best approach to reduce maternal and fetal risks, including macrosomia. However, additional factors may contribute to the excessive rate of macrosomia observed in IDDM pregnancies, despite apparently good glycemic control. It remains to be determined whether refining the management of diabetes in pregnancy will reduce this risk.

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