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Effect of antenatal betamethasone on blood glucose levels in women with and without diabetes

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ABSTRACT

Objective: To characterize the maternal glycemic response to betamethasone in subjects without diabetes compared to subjects with diabetes.

Study design: Blood glucose levels in 22 gravidae without diabetes and 11 gravidae with diabetes were recorded for 48 h following betamethasone administration for threatened preterm delivery. Maximum blood glucose value and time to maximum value were compared. Area under the curve calculations were used to express the duration and degree of significant hyperglycemia for individual subjects. These summary measures were then correlated to subject characteristics and laboratory values to determine a risk profile of those subjects without diabetes at risk for significant hyperglycemia.

Results: All subjects with diabetes and the majority of those without diabetes had significant hyperglycemia during the study period. Mean maximum blood glucose was higher for those with diabetes (205 mg/dL vs. 173 mg/dL, $p \leqslant 0.01$). Mean time to reach the maximum glucose level was similar for both groups. Result of a glucose tolerance test given immediately prior to betamethasone correlated strongly with amount of time spent with hyperglycemia for subjects without diabetes (rho = 0.59, $p \leqslant 0.01$). Morbidly obese subjects spent less time with hyperglycemia than those with lower body mass indices ($p = 0.03$).

Conclusion: Both subjects with and without diabetes demonstrate significant hyperglycemia after receipt of antenatal betamethasone.

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1. Introduction

The American Congress of Obstetricians and Gynecologists (ACOG) recommends the administration of antenatal steroids to patients at risk of preterm delivery between 24 and 34 weeks gestation because of a known decrease in risk of respiratory distress syndrome, intraventricular hemorrhage, and neonatal death [1–3].

Corticosteroids have a well-described impact on glucose metabolism. Both betamethasone and dexamethasone, the corticosteroids used in pregnancy, increase blood glucose levels by antagonizing and decreasing insulin synthesis as well as increasing gluconeogenesis [4]. For this reason, pregnant patients with diabetes are routinely monitored for pathological changes in blood glucose after receipt of antenatal steroids. Normal pregnancy is characterized by relative insulin resistance and glucose intolerance, therefore the combination of pregnancy and corticosteroids could cause significant disruption of glucose homeostasis even in pregnant women without diabetes.

Previous investigations have demonstrated that the impact of antenatal corticosteroids on glycemic control in pregnant patients without diabetes is shortlived [5–9]; however the critical period of hyperglycemia coincides with the time period when a patient is felt to be at risk for preterm delivery. In studies of maternal glucose infusion in women just prior to delivery, cord blood sampling has demonstrated fetal acidosis with both moderate [10,11] and mild [12] maternal hyperglycemia. Lawrence et al. administered 100 g of glucose or saline to laboring women with ketonuria, and found a significantly decreased fetal pH in women who had been given glucose vs. those who received saline (mean fetal pH 7.26 vs. >7.3, respectively) [12]. Given the potential for fetal compromise in the setting of maternal hyperglycemia, we studied the pattern of glucose response to betamethasone in pregnant women with and without diabetes. We correlated the amount of time with hyperglycemia in subjects without diabetes with the results of a glucose tolerance test administered immediately prior to antenatal corticosteroids. Additional maternal characteristics were also evaluated for associations with hyperglycemia in the mother without diabetes.

2. Materials and methods

This was a planned observational study approved by the Institutional Review Board of Memorial Health Care Systems. We enrolled women who were candidates for betamethasone administration due to risk for preterm delivery for any reason between 24 0/7 and 33 6/7 weeks gestation. Inclusion criteria for subjects with diabetes included parturients with new onset gestational diabetes (White's Classification A1 or A2) or preexisting diabetes up to Class B. Exclusion criteria were age less than 18 years old, pre-existing maternal use of medications that affect glucose metabolism, White's Class C diabetes mellitus or higher, pre-existing adrenal or pancreatic dysfunction, chorioamnionitis or other maternal or fetal infection, and refusal to participate. No patient received tocolysis with beta-mimetic agents. Subjects were recruited consecutively until 30 subjects without diabetes and 15 subjects with diabetes were enrolled.

Per study protocol, subjects without diabetes underwent a non-fasting 50-g glucose tolerance test, followed by a 1-h glucose level. Betamethasone 12 mg was then given intramuscularly, followed by a second 12 mg dose 24 h after the first dose. Subjects with diabetes received the same treatment, but did not undergo a pre-treatment glucose challenge.

The usual protocol of our hospital pharmacy is to place insulin-requiring gravidae with diabetes on intravenous insulin immediately following administration of the first dose of betamethasone in anticipation of altered glucose homeostasis. The study protocol required initiation of intravenous insulin in any subject demonstrating persistent blood glucose levels of $\geqslant$210 mg/dL for one hour. Thereafter intravenous insulin was administered per pharmacy protocol to target a blood glucose level of 70–120 mg/dL. Subjects with insulin-requiring diabetes received their pre-study subcutaneous insulin regimen throughout the study period unless they were transitioned to intravenous insulin for a persistent blood glucose level of $\geqslant$210 mg/dL.

Capillary blood glucose levels were recorded for subjects without diabetes every four hours for 48 h after administration of the first dose of betamethasone, unless they had an abnormal pre-treatment glucose tolerance test result of $\geqslant$140 mg/dL. Women without diabetes with an abnormal test result as well as all subjects with diabetes had blood glucose levels recorded every two hours for 48 h after initiation of betamethasone as per institution protocol. All blood glucose levels were determined by Johnson & Johnson Lifescan SureStep® Flexx® glucometers using a fingerstick blood sample performed by hospital nursing staff. The glucometers were subjected to daily calibration and quality assurance measures. All participants were prescribed a 2200 kilocalorie (kCal) diabetic diet during the study period, with meals and snacks delivered at specified times. Subjects recorded the percent intake of each meal in a diet log.

Demographic and laboratory data collected included maternal age, height, weight, body mass index (BMI) in kilograms/meters^2 (kg/m^2), gestational age, number of fetuses, hemoglobin A1c, and white blood cell count at the time of enrollment. The time of day and reason for administration of betamethasone were also recorded. Statistical analysis was performed using the JMP® 8 statistical package. Maximum blood glucose value and time to maximum blood glucose value were compared between subjects without diabetes and subjects with diabetes using nonparametric Wilcoxon tests.

Significant hyperglycemia was analyzed as two endpoints: as a blood glucose level $\geqslant$140 mg/dL, given the ACOG recommendation that postprandial blood glucose levels in patients with diabetes remain below this value, and as a blood glucose level $\geqslant$160 mg/dL, due to previous reports associating this level of maternal hyperglycemia with fetal acid–base abnormalities [12]. Blood glucose measurements were matched with their time of collection in relation to betamethasone administration and plotted vs. time to construct each subject's profile using GraphPad Prism® statistical software. The total time spent with significant hyperglycemia was determined, as well as an assessment of the degree of