Glucose Intolerance as a Consequence of Oral Terbutaline Treatment for Preterm Labor

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Background. In this case series, glucose regulation is examined prospectively during treatment with terbutaline sulfate for premature labor in women who were (1) previously documented as nondiabetic, (2) found to have gestational diabetes mellitus (GDM), and (3) tested for glucose intolerance while terbutaline was being administered. The glucose profiles of women treated with terbutaline were contrasted with the profiles of nondiabetic women and women known to have GDM who were not in premature labor.

Methods. Subjects tested capillary blood glucose an average of five times a day during terbutaline treatment and for 1 week after terbutaline treatment was discontinued. They used memory-based reflectometers that stored and transmitted self-monitored blood glucose data to a personal computer.

Results. A significant difference ($P = .001$) was found between average fasting glucose values (111 ± 23 mg/dL) for the five nondiabetic subjects treated with terbutaline and values of patients in an historical control group (41 nondiabetic pregnancies [72 ± 22 mg/dL]) who were not in premature labor. The four diabetic subjects and the one subject who had not been previously tested also experienced higher blood glucose levels during tocolytic therapy. Glucose levels returned to preintervention values with the cessation of terbutaline therapy.

Conclusions. It has been previously suggested that terbutaline increases hepatic glycogenolysis, which may aggravate glucose intolerance. This phenomenon, combined with normal pregnancy-induced insulin resistance, may explain abnormal ambulatory glucose patterns in women who are euglycemic before introduction of terbutaline therapy.

Key words. Terbutaline; premature labor; diabetes, gestational; hyperglycemia. *J Fam Pract 1993; 36:25-31.*

Premature labor, the onset of uterine contractions before the 37th gestational week resulting in progressive cervical effacement and dilatation, is a significant public health problem in the United States (270,000 women annually).[1–3] Maternal consequences encompass premature rupture of amniotic membranes with associated endometritis, increased risk of thromboembolism, and prolonged psychological distress. The premature infant is at increased risk for respiratory distress, apnea and bradycardia, intraventricular hemorrhage, sepsis, hyperbilirubinemia, necrotizing enterocolitis, feeding dysfunction, rickets of prematurity, and retinopathy of prematurity.[3,4] Rapid initiation of appropriate interventions may diminish the risk of preterm birth.[1,5]

Therapeutic options for premature labor include bedrest with hydration in combination with tocolytic drugs such as intravenous magnesium sulfate or β-sympathomimetic agents including ritodrine and terbutaline.[1,2] The clinical efficacy, flexibility of dosage required, ease of an administration, and relatively low cost have led to widespread use of terbutaline sulfate for tocolysis.[7,8] Terbutaline is a β_2-adrenergic agonist that stimulates the β_2 receptor in the uterine smooth muscle, thereby activating adenylate cyclase. This enzyme catalyzes the conversion of adenosine triphosphate to cyclic adenosine monophosphate (cAMP). Intracellular cAMP inhibits myosin light chain kinase function, thus preventing uterine smooth muscle contraction.[9,10] β_2-Agonists also stimulate β_2 receptors in the hepatocyte membrane, thereby activating hepatocyte intracellular adenylate cyclase. This raises the hepatocyte level of cAMP, resulting

Submitted, revised, August 5, 1992.

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ISSN 0094-3509

in a cascade effect that activates phosphorylase and leads to the conversion of stored glycogen to glucose.[11] This hepatic sequence can result in maternal hyperglycemia in the absence of other homeostatic mechanisms.[12,13]

Despite the known hyperglycemic action of terbutaline, it has been used as a tocolytic for nondiabetic women as well as in pregnancies complicated by pregestational or gestational diabetes mellitus (GDM). Administration of terbutaline to nondiabetic women has been associated with an increased incidence of neonatal hypoglycemia.[14,15] Some studies have shown that β-mimetics administered intravenously further aggravate the underlying glucose intolerance in women with pregestational diabetes.[16–21] Main and coworkers[22] found that patients receiving standard dosages of terbutaline administered orally for at least 1 week before glucose testing had a higher incidence of diagnosis of gestational diabetes when given an oral glucose tolerance test as compared with control patients. Experience with orally administered ritodrine has not been shown to significantly increase the percentage of women diagnosed with gestational diabetes when tested after taking ritodrine for at least 72 hours.[23] There have been no reports based on ambulatory blood glucose monitoring throughout the duration of orally administered terbutaline in the nondiabetic pregnancy or in the pregnancy complicated by diabetes. In this case series, we sought to characterize glucose regulation prospectively throughout the course of terbutaline treatment in women who (1) were previously documented as nondiabetic, (2) had a diagnosis of GDM, and (3) were tested for glucose intolerance during terbutaline therapy.

Methods

Women hospitalized with premature labor at a community medical center were recruited for the study. All potential participants had premature uterine contractions resulting in progressive cervical effacement or dilatation after the 19th gestational week. The diagnosis of premature labor was made by the patient's attending physician. Gestational age was assessed according to the date of the last menstrual period, ultrasound examination, and early pelvic examination. Terbutaline had been orally administered for at least 24 hours before the patient entered the study. Women who had preeclampsia, pregnancy-induced hypertension, multiple medical problems, a hematocrit of less than 30% (to avoid glucose reflectometer error), a history of drug abuse, or who would be unavailable for follow-up (out-of-state transfers) were excluded.

After informed consent was obtained, a nurse specialist in diabetes instructed all subjects in how to obtain capillary blood samples and in the use of a memory-based glucose reflectometer capable of storing the blood glucose value with the corresponding time and date of the test (Glucometer M, Miles Laboratories Inc, Diagnostic Division, Elkhart, Ind). Subjects were asked to check their capillary blood glucose before each meal, 2 hours postprandial, and at bedtime for the duration of the terbutaline therapy and for 1 week after discontinuation of terbutaline therapy. Periodically, meters were checked against results obtained by an independent laboratory (Yellow Springs Instruments, Yellow Springs, Ohio). Adjustments for whole blood values were made in accordance with the manufacturer's guidelines. Decisions regarding the management of premature labor and any complications were made independent of the investigators. The dosage and duration of the terbutaline treatment were recorded, as were the results of standard glucose testing and their timing in relationship to the onset of premature labor.

All subjects underwent a 1-hour, 50-g oral glucose challenge test (GCT) in which plasma glucose results ≥140 mg/dL were considered abnormal in accordance with the National Diabetes Data Group criteria and hospital standards of practice.[24] Gestational diabetes mellitus was diagnosed by a 3-hour, 100-g oral glucose tolerance test (OGTT). Two plasma glucose values ≥105 mg/dL, 190 mg/dL, 165 mg/dL and 145 mg/dL at 0, 1, 2, and 3 hours, respectively, were considered abnormal.[24] Glucose data from the patient's reflectometer were available to the attending physician throughout the course of terbutaline treatment. Following delivery, infant birthweight, height, and neonatal glucose level were measured and any complications of labor and delivery were recorded.

Characterization of ambulatory glucose measurement was accomplished through downloading the glucose data collected by the subjects to a personal computer using *Ambulatory Glucose Profile* (Figure 1) and *Glucofacts* software programs.[25,26] *Glucofacts* uses the glucose values stored in the reflectance meter to produce summary statistics that provide an overall period mean, number of tests per day, range of blood glucose values, and modal day (Figure 2). The modal day collapses all blood glucose values for a specified period, presenting them as if they occurred on a single "typical" day. The *Ambulatory Glucose Profile* program, using these same data to produce a series of five curves, depicts the relative stability of glucose control, assesses the degree of oscillation in the median curve, and gauges the degree and number of significant changes in metabolic control throughout a modal day. Its use in this study was to provide a means of characterizing the relative stability of blood glucose throughout the period of terbutaline treatment and as a

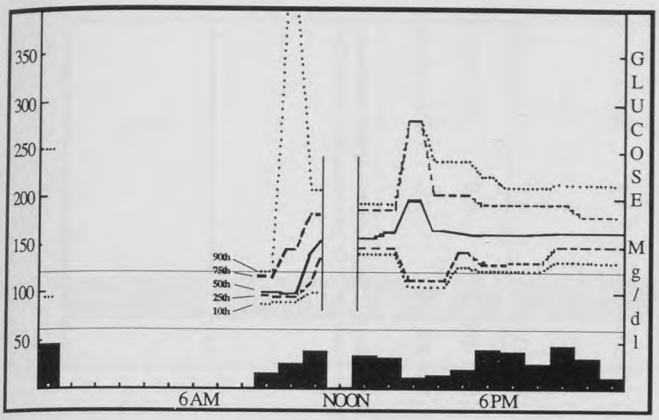

Figure 1. Ambulatory glucose profile (AGP) of a patient during oral terbutaline therapy for premature labor. The five curves represent the 10th, 25th, 50th, 75th, and 90th percentiles of blood glucose values. Using a smoothing algorithm, the AGP calculates each hourly glucose value as if it occurred during a single 24-hour period. Depicted on the *x* axis is a 24-hour clock. On the *y* axis is the blood glucose value based on five capillary samples/day taken over a period of 41 days. The bar graph above the *x* axis represents the relative frequency of testing at each hourly period. No tests were recorded between 12:30 AM and 8:30 AM or between 11:30 AM and 12:30 PM. The largest number of tests were before lunch, before dinner, and after dinner. The horizontal lines from 60 mg/dL to 120 mg/dL represent the normal range of blood glucose values based on nondiabetic controls.

means of comparison with control patients. In previous studies, we found that stability has been closely associated with fetal size and other complications of hyperglycemia in pregnancy.[27]

Results

Twenty-eight women hospitalized with premature labor who met all criteria were asked to participate in the study. Seventeen women declined participation when requested to follow the glucose monitoring protocol. Of the 11 women who consented, one did not report any blood glucose values and was dropped from the study. The remaining subjects tested their glucose levels an average of 5.3 times per day as verified by memory recording in the meter. Clinical characteristics are summarized in Table 1. The age of participants ranged from 19 to 37 years. Three patients were obese before conception, with a body mass index (weight in kg/height in meters squared) greater than 27.3. Onset of premature labor ranged from the 20th to the 33rd gestational week, with an average onset during the 30th week. Terbutaline administration occurred immediately after diagnosis of premature labor in all cases. Initial doses of oral terbutaline ranged from 2.5 mg to 7.5 mg every 3 hours, and ending doses ranged from 7.5 mg every 4 hours to 45 mg every 3 hours. Duration of tocolytic treatment ranged from 8 to 129 days. In eight cases, tocolytic therapy was discontinued electively at 37 weeks' gestation. In the remaining two cases, one subject underwent cesarean section for fetal distress after 34 weeks because of maternal bleeding from a placenta previa, and in the second case terbutaline was withdrawn at 35 gestational weeks after demonstration of fetal lung maturity in a twin gestation.

Classification

Ten women were included in the study. Five women (patients A, F, G, H, and I) were nondiabetic before terbutaline therapy. One woman (J) had a positive GCT and negative OGTT before tocolytic therapy. One woman (B) was found by OGTT to have gestational diabetes before terbutaline therapy. An additional woman (C) underwent OGTT during terbutaline therapy and was found to be diabetic. Two women (D, E) had a positive GCT while being treated with terbutaline. Based on these results (Table 1) five women were classified as nondiabetic because of either a negative GCT or a negative OGTT before tocolytic therapy. Four women were classified diabetic because of a positive OGTT. One woman was classified as unknown because of a positive GCT with no OGTT follow-up while taking terbutaline.

Insulin and Diet Therapy

Treatment for hyperglycemia varied in the study population. Three women in whom GDM was diagnosed

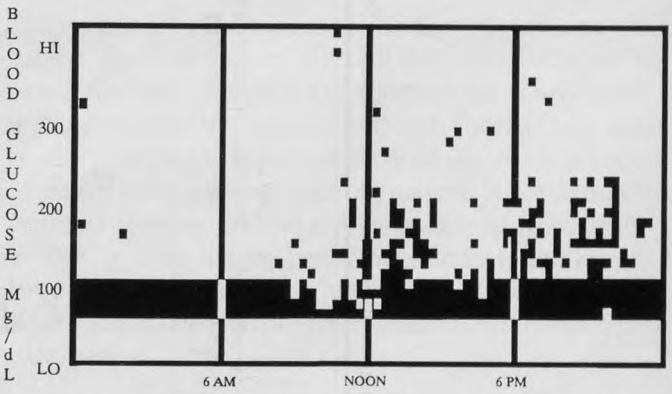

Figure 2. Modal day graph of the blood glucose levels of a previously nondiabetic patient given terbutaline for premature labor. An average of five self-monitored blood glucose tests each day for 41 days is depicted. The *x* axis represents a typical 24-hour period. The shaded area represents the normal range of blood glucose found in patients whose pregnancies were not complicated by diabetes. The points above represent hyperglycemic values.

Table 1. Patient Characteristics and Glucose Results in Study of Terbutaline Therapy for Preterm Labor (N = 10)

Patient	Age (y)	BMI	Gestational Diabetes Mellitus	Onset of Premature Labor (wk)	Terbutaline Therapy (d)	Prior Glucose Challenge Test*	Prior Glucose Tolerance Test*	Current Glucose Challenge Test†	Current Glucose Tolerance Test†	Mean Fasting Glucose Levels of Nondiabetic Women on Terbutaline mg/dL (±SD)	Mean Glucose Levels of Nondiabetic Women on Terbutaline mg/dL (range)	No. of Tests per Day	Treatment
A	19	28.3	Yes	26	42	–	NA	+	+	150 (±52)	136 (86–216)	4.8	Diet/insulin
B	24	21.4	Yes	33	25	+	+	NA	NA	‡	‡	4.2	Diet/insulin
C	23	25.1	Yes	31	36	+	NA	NA	+	77 (±12)	94 (61–135)	4.4	Diet
D	37	34.7	Yes	20	129	NA	NA	+	+	112 (±9)	128 (80–168)	6	Diet/insulin
E	30	22.3	Unknown	25	76	NA	NA	+	NA	176 (±35)	167 (127–235)	6.9	Diet/insulin
F	19	20.6	No	33	23	–	NA	NA	NA	108 (±18)	117 (60–161)	3.2	None
G	21	18.5	No	31	41	–	NA	NA	NA	110 (±22)	118 (65–184)	5	None
H	27	22.4	No	33	8	–	–	NA	NA	90 (±9)	129 (81–193)	4.9	Diet/insulin
I	29	23.5	No	27	33	–	NA	+	–	98 (±8)	150 (100–227)	4.9	Diet/insulin
J	37	27.9	No	30	24	+	–	NA	NA	114 (±0)	118 (93–155)	3.6	Diet/insulin

**Prior glucose challenge test and prior glucose tolerance test indicate whether the patient had this test prior to terbutaline therapy and whether the result was positive (+) or negative (–) for gestational diabetes mellitus.*
†Current glucose challenge test and current glucose tolerance test indicate whether the patient had this test while on terbutaline therapy and whether the result was positive (+) or negative (–) for gestational diabetes mellitus.
‡No data available.
BMI denotes body mass index; NA, not applicable (test was not performed).

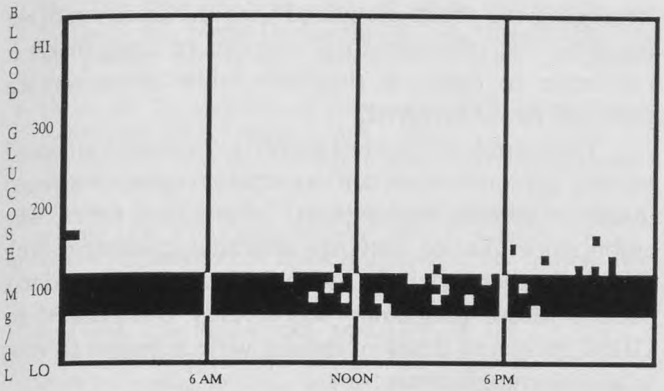

Figure 3. A modal day graph of the blood glucose levels of the same patient as in Figure 2 over a 1-week period following discontinuation of terbutaline therapy. Note the paucity of hyperglycemic events.

were managed with insulin therapy (Table 1). Three women who had been classified as nondiabetic were also treated with insulin therapy on the basis of elevated ambulatory glucose levels. These subjects reported high blood glucose levels immediately following initiation of terbutaline treatment. Although the OGTT result for each of these three women was negative, the ambulatory glucose profiles while receiving terbutaline were interpreted by attending physicians as similar to those seen in the diabetic patients, and thus each patient was managed as if she had GDM.

Glucose Profiles

The ambulatory glucose profile (AGP) and modal day representations of diabetic and nondiabetic women in pregnancy that were developed during a previous study were compared with those produced by subjects in this case series.[29] Depicted in Figure 1 is the AGP of an individual who was nondiabetic when screened at 26 weeks (67 mg/dL plasma glucose). The patient developed premature labor at 31 weeks, and terbutaline therapy was started. It was noted that during terbutaline administration the AGP showed abnormally high blood glucose values throughout the period of treatment when superimposed on the range of blood glucose levels found in the nondiabetic patient. The modal day graphs for the same subject during terbutaline therapy and after discontinuation are shown in Figures 2 and 3. The glucose profile of this patient during terbutaline administration was found to be consistent with the AGP seen in patients with gestational diabetes. The persistently elevated blood glucose values returned to normal ranges after discontinuation of tocolytic therapy and remained normal until delivery 18 days later.

We next compared average fasting glucose values (111 ± 23 mg/dL) for women found to be nondiabetic by standard glucose testing while receiving terbutaline with fasting values in previously studied nondiabetic patients (72 ± 22 mg/dL) who were not in premature labor.[29] The values for subjects treated with terbutaline were found to be significantly higher ($P < .001$). The overall mean blood glucose values of these women taking terbutaline ranged from 117 to 150 mg/dL before insulin therapy (Table 1). It was also noted that 43% to 83% of the glucose values for these subjects were above the standard range for pregnancy (60 to 120 mg/dL). The self-monitored fasting blood glucose values in these nondiabetic subjects before insulin administration were compared with values for untreated GDM control patients (average fasting blood glucoses of 95 ± 22 mg/dL).[29] The fasting blood glucose values for untreated GDM historical control patients were found to be comparable to or lower than fasting blood glucose values for terbutaline-treated nondiabetic patients.

The relationships between glucose patterns and adjustment of tocolytic therapy were examined. In one subject (B) who had preexisting hyperglycemia, blood glucose rose immediately upon terbutaline administration. In all subjects, the drug's tocolytic effect diminished over time, requiring subsequent increases in dosage. Corresponding with this refractory tocolytic effect, a slight improvement in glucose control was found. With the cessation of terbutaline therapy, there was a reduction in glucose levels and, in several cases, a return to normal glycemia.

Method of Delivery and Fetal Outcome

Eleven births were recorded for the 10 subjects (one subject gave birth to twins). All deliveries occurred between the 34th and 39th gestational week. Three infants were delivered by cesarean section (because of frank breech presentation (patient C), fetal distress in a patient bleeding from placenta previa (patient I), or failure to progress (patient D)). Birthweight ranged from 1960 g to 3997 g. Two infants (those of patients C and D) were large for gestational age. Three infants (those of patients B, D, and J) were hypoglycemic in the immediate neonatal period.

Discussion

Hyperglycemia associated with a failure to compensate for increased insulin resistance during pregnancy, as well as an alteration in insulin secretory patterns, has been the hallmark of gestational diabetes.[29] In normal pregnancy,

insulin secretion increases as much as threefold above the baseline for the nonpregnant state.[30] There is also an increase in peripheral insulin resistance, which may promote shunting of ingested carbohydrates to the fetus because of inhibition of maternal glucose utilization. Defects in pancreatic β-cell secretory patterns found in non–insulin-dependent diabetes mellitus (NIDDM) and in GDM may preclude compensation for insulin resistance.[29] Current diagnostic criteria for GDM are based on a statistical definition related to the severity of glucose intolerance and the predictability of subsequent NIDDM.[31]

It has been suggested that, as in NIDDM, a genetic predisposition for developing diabetes is an important factor in GDM. Additional factors in GDM that may contribute to hyperglycemia include human placental lactogen, progesterone, and other gestational hormones.[6,32] Few have considered, however, the introduction of drugs that promote glucose intolerance as an alternative cause of gestational diabetes. This could be the case if women given the "diabetogenic" agent were near the upper percentile of normal carbohydrate tolerance, or were experiencing elevated levels of circulating endogenous catecholamines or corticosteriods resulting from the stress of premature labor. When terbutaline is administered to women in premature labor to counter uterine contractions, the supplemental effect of increased glycogenolysis in the liver may further aggravate glucose intolerance in the previously nondiabetic and gestational diabetic patient. This perhaps was reflected by the increased exogenous insulin required to maintain normal pregnant glucose levels in the group of patients treated with insulin in the current study. One possible explanation is that by increasing hepatic glycogenolysis, terbutaline may induce hyperglycemia, resulting in increased insulin requirements to maintain normal pregnant blood glucose levels. The ensuing hyperinsulinemia may in turn result in downregulation of insulin receptors or an increase in postreceptor insulin resistance or both. These mechanisms for glucose intolerance have been described in gestational diabetes.[6]

This case series raises the question as to whether terbutaline sulfate given orally produces maternal hyperglycemia in previously nondiabetic women and whether the resultant ambulatory glucose profiles can be distinguished from those of patients with GDM. Interestingly, tachyphylaxis seemed to develop within several days of initial terbutaline administration. The development of uterine myometrium tachyphylaxis appears to be less marked, as the tocolytic effect at a particular dose level of terbutaline persists longer than the peak hyperglycemic effect. Desensitization to terbutaline is probably receptor mediated.[11] While it was noted that in all patients the hyperglycemic effects dissipated with the cessation of the tocolytic, the relatively small number of cases makes it premature to conclude that terbutaline alone was the principal factor involved.

The combined effect of tocolytic-mediated increased hepatic glycogenolysis and normal pregnancy-induced insulin resistance may explain, in this case series, why ambulatory glucose patterns appeared consistent with GDM. Further, when the tocolytic was administered to a patient whose pregnancy was already complicated by GDM, increased doses of insulin were required to reestablish normoglycemia.

Should the nondiabetic or the glucose-intolerant woman be treated for premature labor with terbutaline? As already noted, tocolytic therapy must be initiated rapidly to prevent premature birth; therefore, the feasibility of identifying glucose tolerance levels in all women before initiating therapy is low. Short-term consequences of uncontrolled hyperglycemia are not fully understood. In an earlier study of untreated "borderline" hyperglycemia, it was shown that the risk of macrosomia, hyperglycemia, hyperbilirubinemia, and polycythemia are three- to fivefold greater.[28] Maternal risks of toxemia and preeclampsia related to hyperglycemia are not known outside of GDM. It remains unclear whether the infant of a previously nondiabetic mother treated with orally administered terbutaline (resulting in persistent hyperglycemia) is at a similar or greater risk of neonatal and chronic complications as compared with the infant of a woman who has GDM in whom hyperglycemia is not pharmacologically induced.

Clearly, the negative consequences of untreated or poorly treated premature labor are significant.[1–5] Although the case series was limited in size, it raises the question of the efficacy of establishing glucose tolerance in women started on β-sympathomimetic drugs. However, anticipation and treatment of hyperglycemia also raises critical issues. To rapidly achieve euglycemia in pregnancy often requires insulin therapy with daily monitoring of capillary blood glucose. Larger and more extensive studies are needed to fully elucidate the effect of terbutaline on glucose tolerance in pregnancy and to establish appropriate guidelines for detection, monitoring, and treatment of any subsequent hyperglycemia.

Acknowledgment

This study was supported by a grant from the Education and Research Fund of the United Hospital Foundation, St Paul, Minnesota.

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