Effect of Terbutaline Tocolysis on Infant Birthweight

Guy W. Robins, MD; B. Wayne Blount, MD, MPH; and Alfred Arline, MD

Fort Gordon and Atlanta, Georgia, and Fort Lewis, Washington

Background. Previous research has suggested that terbutaline sulfate increases serum glucose in pregnant women. Increases in serum glucose in women who have gestational diabetes mellitus often lead to the birth of larger infants. This study examines the effect on infant birthweight of terbutaline used as a tocolytic agent in otherwise normal term pregnancies.

Methods. An historical cohort study was conducted of all births in a 12-month period at a US Army community hospital. There were 1376 deliveries of all types; 481 of the patients were excluded for variables that influence gestational duration or fetal weight, and 5 patients' records were lost. Birthweights relative to gestational age were compared.

Results. The two groups (women who were treated with terbutaline, n=94; control group, n=796) differed with respect to age (terbutaline group, 1.6 years younger, $P=.002$); pregravid weight (terbutaline group, 10.3 lb lighter, $P<.001$); and total weight gain (terbutaline group, 3.2 lb less, $P=.001$). The groups were comparable in all other variables studied ($P>.05$). Women receiving terbutaline therapy (average length of therapy, 4.7 weeks) gave birth an average of 1 week earlier than those not treated with terbutaline (39.09 weeks and 40.09 weeks, respectively, $P<.001$). The mean absolute birthweight of infants exposed to terbutaline in utero was less than that of infants from the control group ($P<.001$), but this difference (191.6 g) can be accounted for by the difference in average gestational age between the terbutaline group and the control group. There was no difference in birthweight ($P>.05$) when birthweight relative to gestational age was compared between the two groups.

Conclusions. Women in this study who were treated with terbutaline did not give birth to larger infants. The previously noted hyperglycemia in women receiving terbutaline may not have been present in this study population or may not have been significant enough to affect birthweight.

Key words. Tocolysis; terbutaline; birthweight; pregnancy. (*J Fam Pract 1995; 40:581–585*)

Terbutaline has been used as a tocolytic agent in prolonging gestational duration to decrease the incidence of low birthweight infants.[1–7] Although terbutaline's effectiveness as a long-term tocolytic agent has recently come into question,[8] it still enjoys widespread use. Of concern is whether terbutaline use is associated with maternal glucose intolerance.[9–12] Glucose intolerance in gestational diabetes mellitus (GDM) is associated with fetal macrosomia, increased delivery complications, and neonatal hypoglycemia.[13–17] Although research suggests that terbutaline use affects maternal glucose tolerance, its impact on the birthweight of term infants remains largely unexplored.[9–12] The present study examined the relationship between maternal terbutaline use and the birthweight of term infants.

The relationship between terbutaline use and birthweight has not been adequately addressed in the literature to date. Most studies have compared the efficacy of other β-sympathomimetic agents with that of terbutaline.[2] References to birthweight have primarily addressed low birthweight and preterm deliveries.[2,13] One study found

Submitted, revised, July 21, 1994.

Presented in part at the Uniformed Services Academy of Family Physicians Scientific Assembly, 1993, in Corpus Christi, Texas; and at the Georgia Resident Research Day (Family Practice), 1993, in Augusta.

From the Eisenhower Army Medical Center, Fort Gordon (G.W.R.), and Emory University School of Medicine, Atlanta (B.W.B.), Georgia; and Madigan Army Medical Center, Fort Lewis, Washington (A.A.). The views and opinions expressed herein are those of the authors and do not reflect the official policy of the U.S. Army. Requests for reprints should be addressed to Guy W. Robins, MD, Department of Family and Community Medicine, Eisenhower Army Medical Center, Fort Gordon, GA 30905.

ISSN 0094-3509

that terbutaline did not affect birthweight[9]; however, that study was limited by the size of the sample and failure to control for confounding variables.

Using a larger sample and controlling for confounding variables, the present study seeks to evaluate the effect on birthweight of terbutaline used as a tocolytic agent in otherwise uncomplicated term pregnancies.

Methods

In this historical cohort study, all deliveries that occurred in a US Army community hospital during 1991 were reviewed. There were 1376 deliveries of all types. Variables screened during the chart review included maternal age, gravidity, and parity; abortion history; pregravid weight; weight gain during pregnancy; race/ethnicity; estimated gestational age (EGA) when prenatal care began; total number of prenatal visits; tobacco, alcohol, and drug abuse; socioeconomic status; pregnancy dating criteria; type of delivery; complications; birthweight; EGA at birth; medical history; and disqualifying factors.

Military rank of the patient or sponsor was used as an indicator of socioeconomic status. While not ideal, the use of military rank as a proxy for socioeconomic status is commonly used in military studies and frequently is the best surrogate available. Tests that were reviewed included all obstetrical ultrasound findings and 1- and 3-hour glucose tolerance tests. For patients receiving terbutaline therapy, charts were also reviewed for appropriate evaluations of preterm contractions or preterm labor, including cultures of cervix and urine, and antibiotic therapy, if indicated. Preterm contractions were defined as four or more uterine contractions per hour for more than 2 hours, unresponsive to rest and hydration and without cervical change, before 37 weeks' gestation. Preterm labor was defined as uterine contractions resulting in cervical change before 37 weeks' gestation. Dosages of terbutaline were examined as well as EGA when therapy was initiated. Terbutaline dosing was evaluated for total duration of therapy and total terbutaline administered. Infant charts were reviewed for assessment of gestational age and birthweight. Since data were gathered using a retrospective chart review without reference to individual patients, complete anonymity was maintained. Informed consent was not required by the hospital's institutional review committee.

Factors that could affect infant weight or maturity at birth served as study sample disqualifiers (Table 1). Patients who were late in entering prenatal care (after 20 weeks' EGA), as well as patients who were both uncertain of dates and had no obstetrical ultrasound assessment before 22 weeks' EGA, were also excluded from the study. Standard obstetrical dating criteria were followed in assessing gestational age and estimated date of confinement,[18,19] and gestational diabetes mellitus was defined according to standard criteria.[20,21] Specifically, EGA determination was based on the overall best obstetrical criteria, which included last menstrual period, prenatal record of fundal heights (fetal growth), detection of fetal heart rate, ultrasonographic measurements, and neonatal gestational age assessment.

Table 1. Study Sample Disqualifying Factors

Factor	No. Disqualified
Intrauterine growth retardation	14
Gestational diabetes mellitus	53
Preterm delivery (prior to 37 weeks' EGA)	4
Preeclampsia	21
Congenital anomalies	10
Seizure disorders (taking medication)	4
Sickle cell disease or trait	10
Other maternal chronic medical problems	31
Multiple gestations	4
Other tocolytic use	2
Incompetent cervix	6
Uterine anomalies	2
Polyhydramnios	7
Pregnancy-induced hypertension	34
Chronic hypertension	18
Fetal hydrops	5
Trauma	1
Eclampsia	1
Late prenatal care (>20 wk)	188
Uncertain dating of pregnancy	53
Lost chart	15
Incomplete chart	2
Previous delivery within 1 year	1
Total	486

EGA denotes estimated gestational age.

Of the 1376 deliveries, 486 were disqualified by the factors listed in Table 1. Of the patients excluded, only four were disqualified for premature delivery before 37 weeks' EGA. None of the four had been treated with oral terbutaline. Some of the exclusions could be related to both premature contractions and low birthweight and could therefore bias the study's results, but none of the subjects excluded for those reasons in this study experienced preterm contractions or preterm labor.

This study examined the use of terbutaline in women with either preterm contractions or preterm labor in low-risk, uncomplicated pregnancies only. The study sample consisted of 890 uncomplicated pregnancies and deliveries. Of the 890 mothers in the study sample, 94 had terbutaline tocolysis and 796 were untreated.

For the entire sample (N=890) the mean age of the mothers was 24.6 years (standard deviation [SD], 4.65; range, 15 to 41); mean gravidity was 2.16 (SD, 1.22) with a maximum of 9; mean parity was 0.71 (SD, 0.83) with a maximum of 5; mean number of abortions (spontaneous

Table 2. Differences Between Terbutaline Group and Control Group, by Variable

Variable	Terbutaline Group (n=94) Mean (SD)	Control Group (n=796) Mean (SD)	*P* Value	*t* Test
Age, y	23.2 (4.31)	24.8 (4.67)	.002	3.10
Pregravid weight, lb	127.0 (22.0)	137.3 (25.4)	<.001	3.71
Total weight gain, lb	34.2 (10.6)	37.4 (15.1)	.011	2.57
Absolute birthweight, g	3383.7 (518)	3575.3 (462.1)	<.001	3.75
Delivery EGA, wk	39.09 (1.52)	40.9 (1.23)	<.001	6.11

SD denotes standard deviation; EGA, estimated gestational age.

and elective) was 0.45 (SD, 0.83) with a maximum of 6. Thirty (3.4%) of the subject mothers used tobacco or alcohol, or both, during their pregnancies. Socioeconomic class distribution was as follows: lower military rank (E-1 to E-4), 435 (48.9%); middle rank (E-5 to E-8, O-1 to O-3, warrant officers), 427 (48%); and upper middle rank (O-4 to O-6), 28 (3.1%). The racial/ethnic breakdown was 65.5% white, 15.3% black, 10.6% Hispanic, 4.3% Asian, and 4.3% other.

Gestational size was defined as falling into one of three categories: appropriate for gestational age (AGA) characterized neonates between the 10th and 90th percentiles in weight; small for gestational age (SGA) defined neonates under the 10th percentile in weight; and large for gestational age (LGA) referred to neonates over the 90th percentile in weight.

Mean EGA at delivery and mean birthweight for the terbutaline group and the control group were compared by *t* test for independent samples, and birthweight relative to gestational age (SGA, AGA, or LGA) was compared by chi-square. The terbutaline tocolysis group (n=94) and the cohort control group (n=796) were compared for significant differences in all studied confounding variables by *t* test for interval data and chi-square for categorical data. Multiple regression was also used to assess the impact of the independent variables on the dependent variable, birthweight. The independent variables were those with significant differences by chi-square or *t* test: pregravid weight, maternal weight gain, fetal age, and total terbutaline dose. Power analysis revealed that this study (α=.05, N=890) had a power of .88 for detecting a small effect size and a power of .99 for detecting a medium or large effect size in birthweight relative to EGA.

Results

The mean pregravid weight of all 890 study subjects was 136.3 lb (SD, 25.2), and the mean total weight gain 37.13 lb (SD, 14.7). Types of deliveries included 75.4% normal spontaneous vaginal delivery, 8.7% vacuum-assisted, 2.8% forceps, and 13.1% cesarean section. Prenatal care began at a mean of 12.9 weeks' EGA (SD, 4.3) with a mean number of prenatal visits of 11.7 (SD, 2.9). Overall mean delivery EGA was 39.99 weeks (SD, 1.3) with a mean birthweight of 3555.68 g (7.8 lb) (SD, 471.95). Of the 890 infants, 637 (71.6%) were AGA, 244 (27.4%) were LGA, and 9 (1%) were SGA.

In this sample, 94 (10.6%) of the women were placed on oral terbutaline tocolysis, for preterm labor and preterm contractions, with a mean starting EGA of 32.1 weeks (SD, 3.4) and an earliest starting EGA of 23 weeks. Fourteen of these women (14.9%) had their terbutaline doses adjusted at a mean of 33.2 weeks EGA (SD, 3.3). Terbutaline treatment was discontinued at a mean of 36.7 weeks EGA (SD, 1.55). The standard of care for the study hospital was to discontinue tocolytic therapy at 37 weeks' EGA. The mean duration of terbutaline therapy was 4.7 weeks (SD, 3.18) with a maximum duration of 14 weeks. The mean of the total terbutaline dose was 941.5 mg (SD, 695.8) with a minimum of 30 mg and a maximum of 3920 mg over the total duration of terbutaline tocolytic therapy. There were no patients who were placed on terbutaline tocolysis and later found to have GDM.

The two groups were similar ($P>.05$) in the majority of potentially confounding variables studied, including gravidity, parity, number of prenatal visits, when prenatal care began, number of abortions, tobacco or alcohol use, race/ethnicity, socioeconomic status, birth complications, type of delivery, and primary obstetrical provider (obstetrician or family physician). There were differences in the study and control groups, however, with respect to age, pregravid weight, total weight gain, absolute birthweight, and delivery EGA (Table 2). The mean age of the terbutaline group was 1.6 years less than that of the control group. The mean pregravid weight of the terbutaline group was 10.3 lb less than that of the control group, and

the total weight gain was 3.2 lb less in the terbutaline group than in the control group.

The final two differences between the two groups were mean absolute birthweight and mean delivery EGA. The mean absolute birthweight of infants born to women receiving terbutaline therapy was 191.6 g (0.42 lb) less than that of the control infants. However, there was no difference in birthweight when weight relative to gestational age (SGA, AGA, and LGA) was compared between the two groups ($P>.05, \chi^2=1.45$). This lack of difference persisted even when analyzed for a dose-response effect: even at higher total doses of terbutaline or with longer durations of therapy, there was still no effect.

Multiple regression analysis revealed that three variables accounted for birthweight variance: final EGA of the infant, pregravid weight of the mother, and total weight gain of the mother. Together, these three accounted for 21.7% of the variance of the final birthweight of the infants. If the terbutaline dose is forced into the equation, it accounts for only an additional 0.023% of the variance, which is not significant.

Discussion

Oral terbutaline tocolysis can lead to glucose intolerance in pregnant women. This effect is not seen with other oral tocolytic agents.[5] In other conditions that involve impaired glucose tolerance, such as GDM, increased birthweight is a complication as often as 20% of the time.[15,16] However, this study showed no increase in birthweight relative to gestational age with terbutaline use as compared with normal, untreated pregnancies. Overall, mean birthweight in the terbutaline group was 191.6 g less than that of the control group. This difference may be accounted for by the shorter (by 1 week) mean gestation in the terbutaline group. Although the weight difference (6.7 oz) between the two groups in this study was statistically significant, it would not be clinically relevant. Most important, there was no statistically significant difference in birthweight between the two groups when controlling for gestational age: oral terbutaline did not affect the relative number of SGA, AGA, or LGA neonates. Furthermore, analysis by multiple regression demonstrated that terbutaline use does not affect the final birthweight of term infants.

Further study concerning the actual effect of terbutaline on maternal glucose intolerance in conjunction with birthweight is warranted. It might be that this study population did not experience the expected glucose intolerance previously noted in the literature, or that the elevated serum glucose was too transient to have an effect on birthweight.[22] Also, there may be factors in addition to maternal hyperglycemia that lead to fetal macrosomia in GDM.

Studies of terbutaline and glucose metabolism have demonstrated significant alteration of maternal serum glucose levels but differ sharply as to actual incidence of GDM in terbutaline-treated women.[9,10] Main et al[9] examined the birthweight of neonates exposed to long-term terbutaline therapy but found no statistically significant size differences. That study design did not allow adequate examination of confounding variables affecting birthweight, however. Despite the effects of glucose intolerance on birthweight in mothers who had GDM, oral terbutaline therapy in both the study of Main and colleagues and this study did not result in larger infants in otherwise uncomplicated pregnancies. Terbutaline tocolysis, therefore, does not contribute to the complications of fetal macrosomia.

This study retrospectively compared pregnant women who were treated with a tocolytic agent with women who had apparently normal pregnancies. A better study design would be prospective and would include a control group of women with contractions but without tocolytic therapy (as has been done with ritodrine).[23] However, the ethical implications of conducting such a study might render it infeasible. Also, this study is limited to normal pregnancies and addresses fetal size and age issues only in pregnancies reaching term. Issues involving premature delivery with terbutaline tocolysis and neonatal glucose metabolism after in utero exposure to terbutaline were not explored. Finally, the study population was limited to active-duty military personnel and military dependents with normal pregnancies. This group was not representative of the general population for a number of reasons, including open access to prenatal care and a low rate of pregnancies in young teenagers. These findings, therefore, should not be generalized until they have been confirmed in other populations, possibly with prospective randomized studies.

Conclusions

In this study population, the use of oral terbutaline for tocolysis in otherwise uncomplicated pregnancies is not associated with the delivery of larger neonates.

Acknowledgments

The authors wish to thank Glen Markenson, MD, Department of Obstetrics and Gynecology, Perinatology, Madigan Army Medical Center, Fort Lewis, Washington, for assistance in formulating the research questions and gathering the research data, and Christine Philput, PhD, for assisting with statistical analyses.

References

1. Brown SM, Tejani NA. Terbutaline sulfate in the prevention of recurrence of premature labor. Obstet Gynecol 1980; 57:22–5.
2. King JF, Grant A, Keirse MJNC, Chalmers I. Beta-mimetics in preterm labor: an overview of the randomized controlled trials. Br J Obstet Gynaecol 1988; 95:211–22.
3. Fischer JR, Kaatz BL. Continuous subcutaneous infusion of terbutaline for supression of preterm labor. Clin Pharm 1991; 10:292–6.
4. Ridgeway LE, Muise K, Wright JW, Patterson RM, Newton ER. A prospective randomized comparison of oral terbutaline and magnesium oxide for the maintenance of tocolysis. Am J Obstet Gynecol 1990; 163:879–82.
5. Cartis SN, Darby MJ, Chan L. Pharmacologic treatment of preterm labor. Clin Obstet Gynecol 1988; 31:635–51.
6. Cartis SN, Toig G, Heddinger LA, Ashmead G. A double-blind study comparing ritodrine and terbutaline in the treatment of preterm labor. Am J Obstet Gynecol 1984; 150:5–10.
7. Roberts JM. Current understanding of pharmacologic mechanisms in the prevention of preterm birth. Clin Obstet Gynecol 1984; 27:592–605.
8. Parilla BV, Dooley SL, Minogue, Socol ML. The efficacy of oral terbutaline after intravenous tocolysis. Am J Obstet Gynecol 1993; 169:965–9.
9. Main EK, Main DM, Gabbe SG. Chronic oral terbutaline tocolytic therapy is associated with maternal glucose intolerance. Am J Obstet Gynecol 1987; 157:644–7.
10. Angel JL, O'Brien WF, Knuppel RA, Morales WJ, Sims CJ. Carbohydrate intolerance in patients receiving oral tocolytics. Am J Obstet Gynecol 1988; 159:762–5.
11. Foley MR, Landon MB, Gabbe SG, O'Dorisio TM, Waxman M, Leard R, Iams JD. Effect of prolonged oral terbutaline therapy on glucose tolerance in pregnancy. Am J Obstet Gynecol 1993; 168: 100–5.
12. Regenstein AC, Bellvomini J, Katz M. Terbutaline tocolysis and glucose intolerance. Obstet Gynecol 1993; 81(part I):739–41.
13. Laros RK, Kitterman JA, Heilbron DC, Cowan RM, Tooley WH. Outcome of very-low-birth-weight infants exposed to beta-sympathomimetics in utero. Am J Obstet Gynecol 1991; 164:1657–64.
14. Epstein MF, Nicholls E, Stubblefield PG. Neonatal hypoglycemia after beta-sympathomimetic tocolytic therapy. J Pediatr 1979; 94: 449–53.
15. Cowett RM, Schartz R. The infant of the diabetic mother. Pediatr Clin North Am 1982; 29:1213–31.
16. Hollingsworth D. Pregnancy, diabetes and birth. Baltimore, Md: Williams & Wilkins, 1984:132–48.
17. Lindsay MK, Graves W, Klein L. The relationship of one abnormal glucose tolerance test valve and pregnancy complications. Obstet Gynecol 1989; 73:103–6.
18. Attico NB, Meyer DJ, Bodin MJ, Dickman DS. Gestational age assessment. Am Fam Physician 1990; 41:553–60.
19. Smith GN, Frey KA, Johnson TRB. Assessing gestational age. Am Fam Physician 1986; 33:215–20.
20. Gabbe SG, Niebyl JR, Simpson JL, eds. In: Obstetrics: normal and problem pregnancies. 2nd ed. New York, NY: Churchill Livingstone, 1991:1106–7.
21. Cunningham FG, MacDonald PC, Gant NF, eds. Williams obstetrics. 18th ed. Norwalk, Conn: Appleton & Lange, 1989: 818–9.
22. Lindenbaum C, Ludmir J, Teplick FB, Cohen AW, Samuels P. Maternal glucose intolerance and the subcutaneous terbutaline pump. Am J Obstet Gynecol 1992; 166:925–8.
23. The Canadian Preterm Labor Investigators Group. Treatment of preterm labor with the beta-adrenergic agonist ritodrine. N Engl J Med 1992; 327:308–12.