

Continuous subcutaneous terbutaline infusion shows improved clinical outcomes and decreased nursery costs compared with oral tocolytics in women with recurrent preterm labor.

Managing Perinatal Outcomes: The Clinical Benefit and Cost-Effectiveness of Pharmacologic Treatment of Recurrent Preterm Labor

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ABSTRACT

Purpose: To compare the clinical benefit and cost-effectiveness of utilizing continuous subcutaneous terbutaline versus oral tocolytics following recurrent preterm labor.

Design: Retrospective, 1:1 matched cohort.

Methodology: From prospectively collected data in a nationwide, perinatal database of women receiving outpatient services, we identified singleton gestations having recurrent preterm labor, stabilized during hospitalization, and subsequently treated with oral tocolytics (PO group) or continuous subcutaneous terbutaline infusion (SQ group). Those without medically indicated delivery were eligible for inclusion. Each woman in the PO group was matched 1:1 by gestational age at recurrent preterm

labor to a woman in the SQ group. A standardized cost model was applied to compare total antepartum hospital, nursery, and outpatient charges. Wilcoxon Signed Rank, paired *t*, and McNemar's *C*² test statistics were used for comparisons.

Principal findings: 558 women were studied (279 per group). The PO group had less gestational gain following recurrent preterm labor than the SQ group (28.4±19.8 days vs. 33.9±19.0 days, respectively, *P*<.001). The SQ group had less per patient charges (\$) for antepartum hospitalization (3,986±6,895 vs. 5,495±7,131, *P*=.009), and nursery (7,143±20,048 vs. 15,050±32,648, *P*<.001). Outpatient charges were less for the PO group (1,390±1,152 vs. 5,520±3,292, *P*<.001). Overall costs for those in the SQ group were \$5,286 less per pregnancy compared to the PO group.

Conclusion: In this population, continuous subcutaneous terbutaline infusion was both a clinically beneficial and cost-effective treatment following recurrent preterm labor.

Key terms: Health economics, pregnancy, preterm labor, tocolysis, terbutaline, cost-effectiveness, outcomes.

INTRODUCTION

Preterm birth is the most significant cause of perinatal mortality in

much of the world and is a major determinant of neonatal and infant morbidity. The neonatal and long-term health care costs of preterm and low birth weight infants impose a considerable economic burden on individual families, third party payers, and society (St. John 2000; Rolnick 2000).

Total cost of initial neonatal care in the United States for infants born at 24 or more weeks' gestation is estimated at \$10.2 billion annually, with \$9.4 billion spent on surviving infants, and just under \$1.0 billion spent on nonsurvivors (St. John 2000). Preterm infants account for approximately 57 percent of total costs, but only 9 percent of live births (St. John 2000). An infant born at 35 weeks incurs expenses of more than ten times those of an infant born at 38 weeks (\$4,733 vs. \$441), while an infant born at 29 weeks has expenses of more than 10 times those of the infant born at 35 weeks (\$49,540 vs. \$4,733) (St. John 2000). First-year health care charges for infants with even moderately low birth weight (1500 to 2499 grams) are 46 percent higher than infants born at normal birth weight (Rolnick 2000). Approximately 63 percent of total payments for maternal and newborn care are through private, third-party payers, and 17 percent from Medicaid (Long 1994). As such, there is great fi-

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nancial incentive for payers to provide and/or support measures that may prolong gestation in women experiencing preterm labor.

There are generally three pathways leading to preterm birth: spontaneous preterm labor, preterm premature rupture of the membranes (pPROM), and medical induction due to maternal or fetal complicating conditions (Berkowitz 1993). Some prematurity is inevitable, though effective treatment may reduce those related to spontaneous preterm labor.

To effectively decrease the incidence of preterm birth, at-risk women must be identified and frequently evaluated. Success has been reported in preterm birth prevention programs that include one or more of the following interventions: risk assessment, increased prenatal visits, frequent cervical examinations, nursing case management, telemedicine, perinatal home care, patient education regarding the signs and symptoms of preterm labor, and/or early identification of increased uterine contractions (Brooten 2001, Harrison 2001, Alexander 1999, Morrison 2001, Lear 1998, Fangman 1994, Goldenberg 1990, Scheideberg 1997). Virtually any level of proactive, preterm birth prevention will increase prenatal expenditure. This increased maternal cost is often justified through savings in neonatal care expenses and a reduction of prenatal hospital days (Brooten 2001, Harrison 2001, Alexander 1999, Morrison 2001).

When a condition that threatens the continuation of pregnancy to term is diagnosed, such as preterm labor, an effective treatment plan must be initiated. For a treatment plan to be cost-effective, it ideally would decrease the need for antepartum hospitalization, and it would be successful in prolonging pregnancy to allow for fetal maturation, resulting in a decreased need for neonatal intensive care following delivery.

Often, clinicians choose to address the treatment of preterm labor acutely as well as chronically. Initially, after assessing the viability of continuing the pregnancy, the acute episode of preterm labor generally is addressed with intravenous tocolysis. Numerous placebo-controlled studies have demonstrated successful treatment of acute preterm labor with parenteral magnesium sulfate or beta-adrenergic agents (King 1988, Chau 1992, Cotton 1984). In many instances, the symptoms of preterm labor recur before term gestation is achieved. Ongoing tocolysis often is prescribed in an effort to maintain uterine quiescence, control preterm labor symptoms, and prolong gestation.

The beta-adrenergic drug terbutaline often is used for ongoing tocolysis. Efficacy of oral terbutaline is influenced by poor patient compliance and the development of myometrial desensitization related to long-term, high-dose exposure (Berg 1985). Previous investigators have found that continuous low-dose, subcutaneously administered terbutaline may be superior to oral terbutaline for ongoing tocolysis; theoretically, that is due to improved patient compliance and the maintenance of more consistent and therapeutic drug levels (Allbert 1994, Perry 1995). This investigation's purpose is to compare the clinical- and cost-effectiveness of utilizing continuous subcutaneous terbutaline versus oral tocolysis following recurrent preterm labor in women with singleton gestations.

METHODS

The patient population for this retrospective, comparative study was extracted from a large, computerized database (Matria Healthcare, Marietta, Ga.). This database comprises clinical data collected from women from throughout the United States who have been enrolled by their health care provider in outpatient programs related to a high-risk preg-

nancy condition. These outpatient programs and nursing services provide for daily and PRN collection of objective and subjective patient data. Decisions related to treatment — such as route and dosage of tocolytic medications, hospitalization, and timing of delivery — were made solely by the patients' individual health care provider and not by anyone involved in the completion of this study. On enrollment for outpatient services, all women sign informed-consent forms — agreeing to the use of blinded data for research purposes.

From data collected between April 1995 and January 1999, we first identified women meeting the following criteria: 1) singleton gestation, 2) initial episode of preterm labor at greater than 20 weeks, 3) subsequent hospitalization for recurrent preterm labor at less than 35 weeks. Women who were stabilized and later discharged to home following recurrent preterm labor were eligible for study inclusion. We excluded those not prescribed tocolysis, those lost to follow-up, and those who experienced medically indicated delivery. Two treatment groups were then identified: women prescribed oral tocolytics (PO group), and women prescribed subcutaneous terbutaline infusion (SQ group). Prior to compilation of pregnancy/neonatal outcome and cost data, each patient in the PO group was matched 1:1 to a patient in the SQ group by gestational age at the episode of recurrent preterm labor. This match was conducted to control for differences in gestational age at the start of the study period and to provide for a better comparison of treatment efficacy. Parametric data were analyzed using Student's paired *t*. Nonparametric data were analyzed using Wilcoxon Signed Rank and McNemar's *c*². Statistical significance was concluded for two-sided *P*-values <.05.

Women in both groups received ongoing prenatal care from their in-

dividual health care provider. In addition, all participants received outpatient preterm labor management services. These outpatient services consisted of an individual patient-teaching session with a registered nurse regarding the signs and symptoms of preterm labor, and use of a device for electronic collection of uterine activity data. Those in the SQ group received additional education sessions related to infusion-pump use and initiation and care of the infusion site. The outpatient preterm-labor management program included daily nursing assessment of electronically transmitted uterine-activity data and assessment of each patient's clinical condition. The nursing staff was available at all times for patient phone calls and assessment of objective data and subjective patient symptoms. The extent of adherence to both the prescribed medication regime and other physician orders was also assessed, and adherence was encouraged during each nurse-patient contact. On an as-needed basis, the attending physician was notified of changes in a patient's condition by the perinatal nurse. The overall treatment plan — including medication dosing (oral and subcutaneous), antenatal testing, hospital admission, and recommended patient-activity level — was determined by each patient's attending physician.

To evaluate cost-effectiveness, a model was applied wherein charges incurred during the study period for antepartum hospitalization, outpatient services, and nursery days were standardized. In this model, maternal antepartum hospital days were estimated at \$1,000 per day, outpatient-nursing services with continuous subcutaneous terbutaline at \$200 per day, outpatient nursing services with oral tocolysis at \$70 per day, normal newborn nursery at \$500 per day, and neonatal intensive care unit (NICU) at \$2,000 per day. The estimated cost per day for hospital care combines accommodation and ancillary

charges and does not take indirect costs into account. Physician charges, increased first-year, and lifetime medical costs were not considered in the model.

RESULTS

Two hundred seventy-nine women prescribed oral tocolysis (PO group) were matched 1:1 to 279 women prescribed continuous subcutaneous terbutaline (SQ group) following stabilization of recurrent preterm labor. Ninety percent of the population had private insurance, 9.3 percent had Medicaid coverage, and less than 1 percent did not have insurance. Of those with private insurance coverage, approximately half were members of national Aetna, Blue Cross and Blue Shield, Cigna, Prudential, United Healthcare, Humana, or Coventry plans. Maternal demographic and obstetric characteristics are presented in Table 1.

In the PO group, 95.3 percent received terbutaline, with the remaining individuals receiving nifedipine, indomethacin, oral magnesium, or a combination thereof. Almost 32 percent of patients in the PO group received more than one tocolytic medication concurrently. In the SQ group, terbutaline was administered via a microinfusion pump (Minimed Technology, Sylmar, Calif., or Disetronic, Minneapolis, Minn.) that delivered a continuous low-dose basal rate and scheduled bolus doses subcutaneously. Overall, the mean con-

tinuous basal rate was 0.08 mg/hour. Women received a mean of seven boluses per 24-hour period, averaging 0.25 mg per bolus dose. The average daily terbutaline dose was 3.5±1.1 mg for those in the SQ group vs. 24.0±9.3 mg in the PO group.

The mean gestational age at recurrent preterm labor was 31.6±2.2 weeks (matched variable). At the time of recurrent preterm labor, women in the SQ group had been receiving outpatient services for a mean of 24.3±19.3 days versus 25.3±20.4 days for those in the PO group (*P*=.208). Mean days from recurrent preterm labor to a desired goal of term gestation (37 weeks) was 37.5±15.7 days for each group. Women in the SQ group gained an average of 5.5 (95 percent confidence interval 2.7 to 8.3) more gestational days compared to their PO group pair (33.9±19.0 days — SQ group vs. 28.4±19.8 days — PO group). In the SQ group, 47.3 percent achieved at least 37 weeks' gestation, while in the PO group 38.7 percent achieved 37 weeks or more (*P*=.045). Pregnancy prolongation of greater than 2 weeks occurred in 85.7 percent of the SQ group and in 71.3 percent of the PO group.

Pregnancy outcomes are presented in Table 2. The additional days gained by a higher percentage of women in the SQ group resulted in a later mean gestational age at delivery. Related to the later gestational age at delivery, infants of women receiving subcutaneous terbutaline weighed more at

TABLE 1 Maternal characteristics

	Oral (n=279)	Subcutaneous (n=279)	P-value
Age (y)	26.5±6.4	28.2±5.3	.555
Married	69.2%	84.2%	<.001
Smoker	9.7%	4.3%	.012
Gravidity (#)	2.7±1.7	2.5±1.6	.073
Previous preterm delivery	38.0%	29.4%	.017
Cerclage	8.2%	7.5%	.883
GA at first preterm labor	28.0±3.2	28.2±3.0	.208

All data mean±standard deviation or percentage, as indicated.

TABLE 2 Pregnancy outcome

	Oral (n=279)	Subcutaneous (n=279)	P-value
GA at delivery	35.7±2.8	36.5±2.1	<.001
<32.0 weeks	10.8%	2.5%	<.001
<35.0 weeks	30.1%	19.4%	<.003
Cesarean delivery	15%	16.5%	.737
Birth weight	2676 ± 667	2941 ± 556	<.001
<2500 g	38.0%	20.8%	<.001
<1500 g	6.1%	1.4%	.003
Total nursery days	8.7 ± 16.0	4.9 ± 9.8	.005
Median (min,max)	2 (1,120)	2 (0,109)	
NICU (Level III) admit	26.2%	18.6%	.003
Ventilator required*	26.3%	24.2%	.636†

* For those with neonatal intensive care unit (NICU) admission only.

† Pearson's chi-square.

Mean±standard deviation

birth and had fewer nursery days. Overall, 29 percent fewer infants were admitted to the NICU (Level III nursery) from the SQ group. For infants admitted to the NICU, those from the SQ group had a later gestational age at delivery (34.4±2.3 weeks vs. 33.2±2.8 weeks, *P*=.006), higher birth weights (2466±565 grams vs. 2097±613 grams, *P*<.001), and shorter lengths of NICU stay (14.1±17.7 days versus 21.0±22.5 days, *P*=.029) than infants admitted to the NICU from the PO group.

There was one unexplained still-born in the SQ group at 33.1 weeks and no perinatal mortality in the PO group. There were no reported ma-

ternal morbidities in women of the SQ group. One woman in the PO group developed pulmonary edema during hospitalization and treatment with intravenous magnesium sulfate at 30.7 weeks. There were no maternal deaths.

The three main components of estimated total pregnancy charges are shown in Table 3. Both the estimated mean and median total cost for a singleton pregnancy experiencing recurrent preterm labor was higher in the PO group. Nursery costs were the single largest contributor to total pregnancy costs for both groups. The second largest cost contributors were outpatient-nursing costs for the SQ

TABLE 3 Estimated charges (U.S. dollars)

	Oral (n=279)	Subcutaneous (n=279)	P-value
Antepartum hospitalization	5,495±7,131	3,986±6,895	.009
Outpatient services	1,390±1,152	5,520±3,292	<.001
Nursery	15,050±32,648	7,143±20,048	<.001
Total maternal and infant charges*	21,935±33,107	16,649±21,701	.017

* Per patient. Physician and delivery charges not included.

Mean±standard deviation

group and antepartum hospital days for the PO group. Following hospitalization and treatment for the recurrent preterm labor episode, which determined the patient groups, those in the SQ group required fewer hospital days than did those in the PO group (4.0±6.9 days vs. 5.5±7.1 days, *P*<.001).

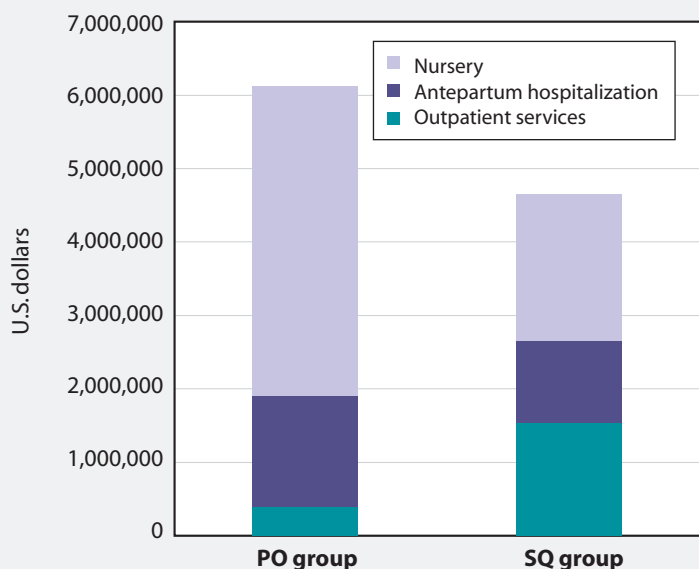
Prenatal and newborn care for these 558 singleton pregnancies complicated with recurrent preterm labor totaled over \$10.7 million. Figure 1 shows the sum of overall estimated charges, presented by treatment group. An estimated \$4.6 million was spent for outpatient nursing services, antepartum hospitalization, and newborn care for the 279 women in the SQ group versus more than \$6.1 million for the 279 women in the PO group. Overall costs averaged \$5,286 less per pregnancy for those in the SQ group versus the PO group.

DISCUSSION

The consequences of prematurity and low birth weight include neonatal mortality, acute morbidity, and/or lifelong neurodevelopmental handicaps (Ettner 1997/98). Morbidities associated with preterm delivery often result from the lack of fully mature respiratory, neurologic, and/or gastrointestinal systems. Immaturity in any or all of these organ systems places the infant at high risk and may result in the need for prolonged and/or specialized medical care (Malone 1999). The sequelae of prematurity also have considerable short-term, as well as long-term, financial ramifications for both the parents and society as a whole. Indeed, compared to infants born of normal birth weight, even infants born with only moderately low birth weight experience an increased rate of re-hospitalization in their first year of life, as well as 46 percent higher medical care charges (Rolnick 2000).

Tocolytic medications are used widely to treat increased uterine contractions associated with preterm

FIGURE 1 Comparison of charges



labor. In fact, the use of tocolysis increased by 50 percent between 1990 and 1999 (Ventura 2001). The rationale for using tocolytics is to inhibit uterine contractions and prolong pregnancy. Delaying delivery with tocolytics may allow the natural neonatal developmental process to take place, the administration of corticosteroids to enhance fetal lung maturity, or can allow for *in-utero* transfer to a facility that is better equipped to care for extremely preterm infants. Thus, even a modest 48-to-72-hour delay in delivery may affect neonatal as well as financial outcomes.

Our goal was to evaluate the clinical outcome and cost-effectiveness of treating recurrent preterm labor with continuous subcutaneous terbutaline versus oral tocolytic medication. In this study, we identified that women treated with continuous subcutaneous terbutaline had greater pregnancy prolongation with better neonatal outcomes than women who were treated with oral tocolytics. In the population studied, the benefits of improved neonatal outcomes far outweighed the higher costs related to outpatient treatment with continu-

ous subcutaneous terbutaline. We acknowledge that the retrospective design of this analysis, as well as the lack of a placebo control group, limits the generalization of our study results to other patient populations. It is important to note, however, that our focus was on treatments initiated in an extremely high-risk group of patients, following hospitalization for an episode of recurrent preterm labor, and our study design was such that patients were matched 1:1 via a random selection method by their gestational age at recurrent preterm labor.

In our investigation, a cost model was designed due to the nationwide distribution of study patients, the difficulty of obtaining actual charge data from inpatient facilities, and the 4-year study period. This model was created to eliminate regional and contractual variations in charges and to equalize the inflationary impact. Only charges occurring after recurrent preterm labor were analyzed. Physician charges were not included in this analysis.

Our model is conservative in many aspects. Antepartum hospital costs

were calculated at \$1,000 per inpatient day. In fact, this is considerably less than what is found in other reports in the literature for antepartum hospitalization charges, which average approximately \$1,400 to \$2,100 per day (Haas 1996, Scott 1997), as well as government estimates provided by the Agency for Healthcare Research and Quality (AHRQ) through the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample for 1997, which estimated nationwide inpatient charges for preterm labor at \$1,789 per day. In determining antepartum charges, we did not include charges for hospital observation admissions of less than 24 hours, which may have decreased the overall estimated charges for inpatient care. Data released by HCUP and provided by the Nationwide Inpatient Sample for 1997 estimated a mean charge of \$2,318 per day for infants with the diagnosis of low birth weight; \$2,749 per day for those with respiratory distress syndrome; \$1,151 per day for those born preterm, but without major problems; and \$590 per day for normal newborn care. In our model, costs for normal newborn nursery and NICU were conservatively estimated at \$500 per day and \$2,000 per day, respectively.

In this analysis, overall savings were realized through a reduction in NICU utilization and overall nursery days for infants in the SQ group. This is supported by previous work, which has shown substantial improvement in neonatal outcome and decreased costs related to higher birth weight and later gestational age at delivery (Ettner 1997/98, Malone 1999). Though there are apparent savings in antepartum hospital charges for those receiving subcutaneous terbutaline, there was actually a cost shift to outpatient services. When combining mean charges for antepartum hospitalization and outpatient services, the total for each group is similar.

We believe that the greater pro-

longation of pregnancy and better neonatal outcomes in this subcutaneous terbutaline group may be related to more precise dosing of terbutaline afforded by the programmable, microinfusion pump, a reduced incidence of myometrial desensitization (tachyphylaxis), and improved patient tolerance and compliance when terbutaline is administered subcutaneously.

The clinical safety and efficacy of terbutaline as a tocolytic has been studied, with varied results. While intravenous terbutaline has been shown to be effective in delaying delivery when used to treat an acute episode of preterm labor (King 1988), prolonged use of tocolytics to maintain uterine quiescence continues to be studied (Lewis 1996, Rust 1996, Sanchez-Ramos 1999). Nonetheless, many health care providers prescribe ongoing tocolysis after stabilization of acute preterm labor attempting to control uterine activity, decrease the incidence of recurrent preterm labor, and further prolong pregnancy. When preparing an ongoing treatment plan for a high-risk pregnancy complicated by recurrent preterm labor, a physician will often consider the gestational age of the pregnancy, and patient response and tolerance of previously prescribed tocolytic agents, as well as case-management recommendations and third-party payer guidelines.

Oral terbutaline often is prescribed for ongoing tocolysis. Frequent dosing, sleep disruption, and patient discomfort related to common side effects, which include tachycardia, headache, nausea, shakiness/tremors, and/or feelings of anxiety, contribute to patient noncompliance and limit the usefulness of oral administration. In addition, the high doses required for maintaining uterine quiescence often lead to desensitization of uterine beta-receptors, resulting in tocolytic breakthrough and recurrent preterm labor (Berg 1985).

In 1988, we described our experi-

ence using a microinfusion pump to administer a low-dose basal rate and scheduled bolus doses of subcutaneous terbutaline on nine women with recurrent preterm labor. Pregnancies were prolonged an average of 9.2 ± 4.3 weeks in this population (Lam 1988a). In randomized fashion, we also reported on 68 patients who received either continuous subcutaneous terbutaline, or oral terbutaline, following stabilization with intravenous tocolysis. In this study, those receiving subcutaneous terbutaline had their pregnancies prolonged a mean of 8.6 weeks, compared with a mean of 2.4 weeks in the oral terbutaline group (Lam 1988b). More recently, we compared gestational days gained with oral terbutaline to days gained with subcutaneous terbutaline in twin pregnancies. In that population, women gained a mean of 19.3 days on oral terbutaline prior to recurrent preterm labor, with a subsequent mean gain of 34.0 days with continuous subcutaneous terbutaline (Lam 2000). In another study of twin gestations with recurrent preterm labor, we reported a savings of \$17,109 in pregnancies treated with continuous subcutaneous terbutaline versus oral tocolysis (Lam 2001).

Others also have compared continuous subcutaneous terbutaline to oral terbutaline for ongoing tocolysis following recurrent preterm labor. Allbert and his team of investigators, in a matched study design, compared 32 patients who received subcutaneous terbutaline infusion to 32 patients who received oral therapy (Allbert 1994). They concluded that continuous subcutaneous terbutaline appeared to be more successful in prolonging gestation than oral therapy. Singleton and multiple gestations were combined. Women achieved 72 percent of desired prolongation with oral therapy compared to 86 percent desired prolongation for those receiving subcutaneous therapy. Moise et al reported on 13 patients given continuous subcutaneous terbutaline

following failure of other tocolytic regimens (Moise 1992). Though the investigators considered their findings to reflect only limited success, pregnancies were extended an average of 35 days.

Studies also have been performed using continuous subcutaneous terbutaline for prophylactic tocolysis in higher order multiple gestations (Elliott 1997), and in protocols where women were given much lower doses of terbutaline than described in the current study, and did not receive supplemental outpatient nursing services (Wenstrom 1997, Guinn 1998).

The present study is the first of its kind to compare outcomes of singleton pregnancies treated with continuous subcutaneous terbutaline versus oral tocolytics following recurrent preterm labor, and then examine costs related to treatment and outcomes. As such, we demonstrated continuous subcutaneous terbutaline to be a cost-effective, pharmacologic treatment option when compared to oral tocolytics in the treatment of high-risk singleton pregnancies experiencing recurrent preterm labor.

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