TERBUTALINE

To the Editors: We read with interest the study by Guinn et al (Guinn DA, Goepfert AP, Owen J, Wenstrom KD, Hauth JC. Terbutaline pump maintenance therapy for prevention of preterm delivery: a double-blind trial. Am J Obstet Gynecol 1998;179:874-8) regarding subcutaneous terbutaline therapy for prevention of preterm delivery. This study unfortunately tells us nothing about the efficacy of this therapy as it is commonly prescribed by obstetricians. During the study period (November 1994–April 1997) Guinn et al discharged their patients home without daily nursing contact or home uterine contraction monitoring, both of which are the standard of care and are necessary for the use of subcutaneous terbutaline therapy outside the hospital setting. Objective data are essential for individual dosage changes (increased drug delivery during times of documented increased uterine activity), as one would do in the hospital. When daily monitoring and nursing contact have been included, positive efficacy and safety results have been confirmed. Terbutaline dosage in the study of Guinn et al was determined without appropriate consideration of individual body mass index, contraction activity, or cervical status, as is the standard practice. In light of the 3- to 4-hour half-life of terbutaline during pregnancy and the fact that no patients received scheduled drug boluses between 11 PM and 7 AM (usual periods of peak contraction activity), patients were likely to have subtherapeutic drug levels by morning.

Most patients enrolled by Guinn et al were too far advanced in cervical dilatation and effacement to benefit from any maintenance tocolytic therapy. Indeed, in 50% of women receiving terbutaline the cervix was ≥3 cm dilated and ≥50% effaced, with 25% of patients having cervical dilatation of ≥4 cm and effacement of ≥70%. Thus patients had little chance of attaining the already optimistic 22-week expected prolongation with respect to placebo. Many subjects were also enrolled late in pregnancy (mean 31 weeks’ gestation), such that the expected pregnancy prolongation of 6 weeks for the terbutaline group was often not even possible because treatment was discontinued per protocol at 36 weeks’ gestation. More troubling is that only recurrent preterm labor at <34 weeks’ gestation was treated, even though 12 patients (23%) were delivered at 34 to 37 weeks’ gestation and might have benefited from tocolysis.

Additionally, 46% of patients in the terbutaline group dropped out of the study. Our experience is to expect a 6% dropout rate when traditional programs delivering this therapy are used. With only 32 patients of this predominantly (94%) public assistance population completing the study, these results can hardly be generalized to other patient populations as Guinn et al suggest. Finally, the comments of Guinn et al regarding the published safety data on this therapy neglect the largest published review (n = 8000 cases) of this therapy, which found an extremely low rate of adverse events and no maternal deaths related to this treatment.

We are uncertain why Guinn et al chose such an unconventional delivery of this therapy, except perhaps for their reluctance to use traditional home health programs that offer these services as alternatives to costly inpatient care. Home health programs are routinely used in other fields of medicine. Because so many clinical considerations were ignored by Guinn et al, it seems that the study was undertaken specifically to show a lack of benefit from this therapy.

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REFERENCES

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Reply

To the Editors: We appreciate the interest expressed by Elliott et al in our report and welcome the opportunity to respond to their comments and their personal use of this unproven technology. These investigators make several points regarding our study design. Their first concern is that we studied the terbutaline pump without concomitant home uterine activity monitoring and daily nursing support. Our goal was to determine whether continuous subcutaneous terbutaline administration had independent value. The recently published randomized trial of home uterine activity monitoring of Dyson et al demonstrated beyond reasonable doubt that the use of home uterine activity monitoring does not prevent premature births. The American College of Obstetricians and Gynecologists has consistently discouraged the use of home uterine activity monitoring and has sent representatives to speak against the use of this technology at sev-
eral Food and Drug Administration Obstetrics-Gynecology Devices Panel proceedings. Before discharge, our patients were given thorough instructions in self-palpating uterine contractions, and they also had 24-hour access to nursing support.

Their second concern was our pump dosage protocol. Our regimen was essentially the same as that endorsed by Lam in the January 1989 issue of Contemporary OB-GYN. However, the protocol was modified slightly on the basis of the recommendation of a representative of the pump manufacturer (MiniMed, Inc, Sylmar, Calif) who had extensive experience with terbutaline pump therapy and whose job description included training support personnel on the proper use of the pump. Patients were allowed to self-administer boluses if uterine activity was present, and the mean total dose per day which our patients received was almost identical to the dose used by each of the investigators in their “descriptive” studies of terbutaline pump therapy.

Third, Elliott et al suggest that our patients’ labor was in general too advanced when it was arrested with par enteral tocolysis to allow them to benefit from maintenance therapy. Are Elliott et al suggesting that we not use pump therapy for women who have dilatation of ≥3 cm? Elliott et al have never suggested in any of their publications that pump therapy is not efficacious in women with cervical dilatation of ≥3 cm. Our study was specifically designed to include only women who met previously determined criteria for preterm labor, and we were understandably reluctant to enroll women who had only preterm contractions. Patients who are at highest risk for preterm delivery would logically be the best candidates for maintenance therapy. We believe that our observed lack of efficacy in this population is far more telling than would be data from women at lower risk of preterm delivery. It appears that Elliott et al are selectively expressing concerns that support their personal biases. Furthermore, it is our institutional practice to withhold parenteral tocolysis from women at ≥34 weeks’ gestation because the risk of major neonatal morbidity at this gestational age is minimal. All the neonates who were delivered between 34 and 37 weeks’ gestation did well.

Fourth, the investigators expressed concern that our dropout rate was substantial and that our population was composed largely of indigent women. Does the fact that our patients were predominantly receiving public assistance make our findings less credible? The dropout rates in both the terbutaline and the placebo groups were high. When we compared the outcomes of the women who continued terbutaline pump therapy with those of the women who continued placebo therapy until delivery, active pump therapy resulted in a 2-day-longer prolongation of pregnancy, a clinically insignificant difference.

We concur with the final point of Elliott et al that the rate of major adverse effects with terbutaline pump therapy is low; however, serious complications (including a maternal death) have been reported. We do not believe that any adverse effects are acceptable if an expensive technology with no proven benefit has been used outside properly designed clinical trials.

We understand that Elliott et al have published extensively on their experience with terbutaline pump therapy, but they have published no randomized double-blind trials in peer-reviewed journals that confirm the effectiveness of this treatment. Descriptive studies without appropriate controls do not provide sufficient evidence on which to base expensive and occasionally hazardous therapeutic recommendations. Although we agree that no study is perfect, the current weight of controlled clinical evidence does not support the efficacy of the terbutaline pump for maintenance therapy after preterm labor arrest with parenteral tocolytic therapy. Clearly, the American College of Obstetricians and Gynecologists and the Food and Drug Administration agree with these conclusions. Once again, we urge Elliott et al to demonstrate, in properly designed randomized, controlled trials, a role for terbutaline pump therapy in preventing or reducing premature birth.

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REFERENCES

Reply
To the Editors: Morrison has been a leading proponent of the technology of home uterine activity monitoring with or without the addition of subcutaneous terbutaline pump tocolytic therapy. I therefore welcome the opportunity that his group has provided to again point out the following: (1) Daily nursing contact or daily home uterine contraction monitoring is not the standard of care. (2) Elliott et al must provide data from prospective randomized double-blind trials published in peer-reviewed journals to prove the effectiveness of the terbutaline pump, with or without home uterine activity monitoring. (3) Elliott et al must provide similar data regarding the effectiveness of subcutaneous terbutaline therapy with consideration of individual body mass index, contraction activity, contraction status, and time-of-day dosage sched-