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Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate

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ABSTRACT

BACKGROUND

Women who have had a spontaneous preterm delivery are at greatly increased risk for preterm delivery in subsequent pregnancies. The results of several small trials have suggested that 17 alpha-hydroxyprogesterone caproate (17P) may reduce the risk of preterm delivery.

METHODS

We conducted a double-blind, placebo-controlled trial involving pregnant women with a documented history of spontaneous preterm delivery. Women were enrolled at 19 clinical centers at 16 to 20 weeks of gestation and randomly assigned by a central data center, in a 2:1 ratio, to receive either weekly injections of 250 mg of 17P or weekly injections of an inert oil placebo; injections were continued until delivery or to 36 weeks of gestation. The primary outcome was preterm delivery before 37 weeks of gestation. Analysis was performed according to the intention-to-treat principle.

RESULTS

Base-line characteristics of the 310 women in the progesterone group and the 153 women in the placebo group were similar. Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation (incidence, 36.3 percent in the progesterone group vs. 54.9 percent in the placebo group; relative risk, 0.66 [95 percent confidence interval, 0.54 to 0.81]), delivery at less than 35 weeks of gestation (incidence, 20.6 percent vs. 30.7 percent; relative risk, 0.67 [95 percent confidence interval, 0.48 to 0.93]), and delivery at less than 32 weeks of gestation (11.4 percent vs. 19.6 percent; relative risk, 0.58 [95 percent confidence interval, 0.37 to 0.91]). Infants of women treated with 17P had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen.

CONCLUSIONS

Weekly injections of 17P resulted in a substantial reduction in the rate of recurrent preterm delivery among women who were at particularly high risk for preterm delivery and reduced the likelihood of several complications in their infants.

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PRETERM DELIVERY — THAT IS, DELIVERY before 37 completed weeks of gestation — is the major determinant of infant mortality in developed countries.¹ Preterm delivery is more common in the United States than in many other developed countries and is the factor most responsible for the relatively high infant mortality in this country.¹ The rate of preterm delivery in the United States has increased progressively from 9 percent to 12 percent over the past two decades.² Despite many trials of reduced activity, tocolytic therapy, antibiotic therapy, and other strategies for prevention, no effective and reproducible method of preventing preterm delivery has been demonstrated.³

One treatment that showed promise in small trials was prophylactic treatment with progestational compounds.⁴⁻⁷ Not all trials reported positive results.^{8,9} One meta-analysis found no evidence of effectiveness of progestational compounds in the prevention of preterm delivery or the prevention of recurrent miscarriage.¹⁰ Another meta-analysis, restricted to trials of 17 alpha-hydroxyprogesterone caproate (17P), a natural metabolite of progesterone, showed, in composite, a significant reduction in the rate of preterm delivery.¹¹ We therefore chose this pharmacologic agent as the active drug for our study.

Women who have had a preterm delivery are at especially high risk for preterm delivery in a subsequent pregnancy.¹² We therefore conducted a multicenter trial to test the effectiveness of 17P as compared with placebo in the prevention of recurrent preterm delivery in this group of women.

METHODS

SUBJECTS AND SCREENING

Medical records of women presenting for prenatal care at the 19 participating centers were screened for eligibility to participate in the trial; criteria for eligibility included a history of spontaneous preterm delivery in a previous pregnancy and a current pregnancy between 15 weeks and 20 weeks 3 days of gestation. Reasons for exclusion were multifetal gestation, known fetal anomaly, progesterone or heparin treatment during the current pregnancy, current or planned cervical cerclage, hypertension requiring medication, a seizure disorder, or a plan to deliver elsewhere. An ultrasonographic examination was required between 14 weeks and 20 weeks 6 days of gestation to confirm the duration of gestation and to identify any major fetal anomalies. The duration

of gestation at the time of randomization was determined according to a previously described algorithm¹² on the basis of the last menstrual period and the results of ultrasonography.

Candidates for the trial were approached by a research nurse, who explained the study and asked prospective participants to sign a form for the release of medical records to permit the research nurse to obtain a copy of the chart from the previous pregnancy ending in preterm delivery. If the previous preterm delivery was of a liveborn singleton infant between 20 weeks of gestation and 36 weeks 6 days of gestation and was due to spontaneous preterm labor or preterm premature rupture of the fetal membranes, and if no criteria for exclusion were present, the woman was deemed to be eligible for the study. Each eligible woman was then invited to participate and to sign a consent form approved by the local institutional review board.

The trial started in April 1998 but was stopped in February 1999 because the Food and Drug Administration had ordered the pharmaceutical company that supplied the active study drug to shut down and had mandated a total recall of all the company's drugs, including the study drug, because of poor quality control and documentation. Patient safety was not considered to have been compromised, but the potency of the product that had been supplied was thought to be questionable. At the time the study was stopped, 150 women had been enrolled, but none of the data had been analyzed. The trial was started anew with the study drug and placebo supplied by a company that manages investigational drugs (Eminent Services), and the data that had been collected previously were not included in the analyses.

RANDOMIZATION AND FOLLOW-UP VISITS

Consenting women were given a trial intramuscular injection of the inert oil placebo and asked to return in one week for randomization. If a woman did not return for a randomization visit between 16 weeks and 20 weeks 6 days of gestation, she was not permitted to participate in the trial. Returning eligible patients were then assigned to receive identically appearing active (17P) or placebo (castor oil) injections prepared by a research pharmacy. The women, their caregivers, and research personnel were not informed of the study-group assignment.

The boxes of 17P or placebo were packaged for each center according to a randomization sequence prepared by the George Washington University Bio-

statistical Coordinating Center. The urn method of randomization,¹³ with stratification according to clinical center, was used to create the computer-generated randomization sequence. A 2:1 ratio was used for the assignment of women to 17P or to placebo, because it was known that patients assigned to placebo would be receiving painful injections on a weekly basis with no possibility of direct benefit.

After entering the study, the subjects returned for weekly injections of 17P or placebo given by a study nurse; the injections continued until 36 weeks of gestation or delivery, whichever occurred first. In addition to the weekly visits for study injections, the women received prenatal care at their institutions, as judged appropriate by their caregivers for their known level of risk of preterm delivery.

ASSESSMENT OF OUTCOME

After delivery, study personnel reviewed all prenatal, delivery, newborn, and postpartum records and documented the date of delivery, birth weight of the infant, and neonatal course, as well as the occurrence of complications of pregnancy. Infants were followed until discharge from the hospital where they were born or, if they were transferred elsewhere, from the hospital to which they were transferred. Preterm delivery was defined as delivery at less than 37 completed weeks (259 days) of gestation, calculated as delineated above.

STATISTICAL ANALYSIS

The analysis was performed according to the intention-to-treat principle. Continuous variables were compared with the use of the Wilcoxon rank-sum test, and categorical variables were compared with the use of the chi-square or Fisher's exact test (the latter when there was an expected value of less than five for any cell). Prolongation of pregnancy was assessed by life-table methods, with the duration considered being that between the time of randomization and the time a woman gave birth, was lost to follow-up, or reached 40 weeks of gestation, whichever came first. Curves for event-free survival were estimated with use of the Kaplan-Meier method, with adjustment to account for differing durations of gestation at entry, and were tested with the log-rank test.

On the basis of data from a previous study by the Maternal-Fetal Medicine Units Network,¹⁴ we estimated that 37 percent of the women in the placebo group would deliver before 37 weeks of gestation. With the use of this estimate, a total sample size of

500 women (334 in the progesterone group and 166 in the placebo group) was deemed to be sufficient for the detection of a reduction of 33 percent in the rate of preterm delivery (from 37 percent to 25 percent), under the assumptions of a type I error (two-sided) of 5 percent and a power of at least 80 percent. Before the study began, it was decided that the independent data and safety monitoring committee would use the group sequential method of Lan and DeMets,¹⁵ with a spending function for the type I error corresponding to the O'Brien-Fleming boundary, for interim monitoring and adjustment of the type I error. At the second interim analysis, conducted when 463 patients had undergone randomization, outcome data were available for 351 patients (70 percent of the planned sample). The boundary (P=0.015) for the test of significance of the primary outcome, preterm delivery, was found to have been crossed, and enrollment in the trial was halted.

RESULTS

CHARACTERISTICS OF THE WOMEN

A total of 2980 women were identified as potentially eligible for the study on the basis of a review of medical records from September 1999 to February 2002. Of these women, 1039 were found to be eligible, and 463 eligible women gave consent for the trial and underwent random assignment to 17P or placebo. The main reasons for ineligibility included lack of documentation of the qualifying preterm delivery (in the cases of 549 women), a gestational age of more than 20 weeks (482 women), and current or planned cervical cerclage (241 women).

The characteristics of the 310 women in the progesterone group and the 153 women in the placebo group are shown in Table 1. The women in the two groups were similar in terms of the mean duration of gestation in the qualifying delivery, the mean duration of gestation at the time of randomization, race or ethnic group, marital status, body-mass index, educational level, smoking status, and substance use during pregnancy. The women in the placebo group had had more previous preterm deliveries (mean, 1.6 vs. 1.4; P=0.007).

COMPLIANCE AND SIDE EFFECTS

Noncompliance was defined by a gap of 10 days or more between any two injections. According to this definition, 91.5 percent of the women were compliant with all of their injections. There was no dif-

Table 1. Characteristics of the 463 Women at Randomization.*

Characteristic	Progesterone Group (N=310)	Placebo Group (N=153)
Duration of gestation at the time of qualifying delivery — wk	30.6±4.6	31.3±4.2
No. of previous preterm deliveries	1.4±0.7	1.6±0.9†
>1 Previous preterm delivery — no. (%)	86 (27.7)	63 (41.2)
≥1 Previous term deliveries — no. (%)	153 (49.4)	71 (46.4)
Duration of gestation at randomization — wk	18.4±1.4	18.4±1.4
Age — yr	26.0±5.6	26.5±5.4
Race or ethnic group — no. (%):‡		
Non-Hispanic black	183 (59.0)	90 (58.8)
Non-Hispanic white	79 (25.5)	34 (22.2)
Hispanic	43 (13.9)	26 (17.0)
Asian	2 (0.6)	1 (0.7)
Other	3 (1.0)	2 (1.3)
Marital status — no. (%)		
Married or living with partner	159 (51.3)	71 (46.4)
Never married	119 (38.4)	64 (41.8)
Divorced, widowed, or separated	32 (10.3)	18 (11.8)
Body-mass index before pregnancy§	26.9±7.9	26.0±7.0
Yr of education	11.7±2.3	11.9±2.3
Smoking during pregnancy — no. (%)	70 (22.6)	30 (19.6)
Alcohol use during pregnancy — no. (%)	27 (8.7)	10 (6.5)
Substance use during pregnancy — no. (%)	11 (3.5)	4 (2.6)

* Plus-minus values are means ±SD.

† P=0.007.

‡ Race was self-assigned by the women.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

ference in the rate of compliance between the two groups. A total of 231 women (50 percent) reported at least one adverse effect. The most common side effects were local injection-site reactions, including soreness (in 34.2 percent of the women), swelling (in 14.1 percent), itching (in 11.3 percent), and bruising (in 6.7 percent). More women in the progesterone group than in the placebo group had swelling at the injection site (17.2 percent vs. 7.8 percent, P=0.007) or a lump at the injection site (5.5 percent vs. 1.3 percent, P=0.03).

PRIMARY OUTCOME AND PRETERM DELIVERY

Outcome data were available for 459 of the 463 women (99.1 percent) (Table 2). The frequency of delivery before 37 weeks of gestation was 36.3 per-

cent in the progesterone group, as compared with 54.9 percent in the placebo group (P<0.001). Delivery before 35 weeks of gestation was also less frequent in the progesterone group (20.6 percent vs. 30.7 percent, P=0.02). There was a 42 percent reduction in the rate of delivery before 32 weeks of gestation in the progesterone group (11.4 percent vs. 19.6 percent, P=0.02). Rates of preterm delivery in the progesterone group did not differ according to the week of gestation at the time of the qualifying delivery. Survival analysis showed a significant prolongation of pregnancy with 17P as compared with placebo (P=0.01). Because there was an imbalance between the progesterone and placebo groups with regard to the number of previous preterm deliveries, we performed an analysis with adjustment for this variable. The adjusted relative risk of delivery before 37 weeks of gestation in the 17P group as compared with the placebo group was 0.70 (95 percent confidence interval, 0.57 to 0.85). There were no significant differences between the two groups in the rates of hospital visits for preterm labor, use of tocolytic drugs, corticosteroid use, cesarean delivery, or chorioamnionitis (Table 2).

More than half the women enrolled were black. The reduction in the rate of preterm delivery with 17P among the black women was very similar to that among nonblack women (Table 2).

The effectiveness of 17P in this study suggests that only 5 to 6 women (95 percent confidence interval, 3.6 to 11.1) with a level of risk for preterm delivery similar to that among these women would need to be treated in order to prevent one preterm delivery before 37 weeks of gestation. Similarly, 12 women (95 percent confidence interval, 6.3 to 74.6) with a similar level of risk would need to be treated in order to prevent one delivery before 32 weeks of gestation.

Rates of spontaneous miscarriage between 16 weeks of gestation and 19 weeks 6 days of gestation, and rates of fetal death after 19 weeks 6 days of gestation are shown in Tables 2 and 3. There was a small and nonsignificant increase in the rate of miscarriages and stillbirths in the progesterone group as compared with the placebo group. With one exception, all stillbirths occurred before 24 weeks of gestation.

OUTCOMES AMONG THE INFANTS

There was a significant reduction in the risk of a birth weight of less than 2500 g in the progesterone group as compared with the placebo group (relative

risk, 0.66; P=0.003) and a nonsignificant reduction in the risk of a birth weight of less than 1500 g (relative risk, 0.62; P=0.08) (Table 3). Treatment with 17P led to significant reductions in the rates of necrotizing enterocolitis (P=0.01), need for supplemental oxygen, and intraventricular hemorrhage of any grade. However, there was no significant difference between groups in the rate of intraventricular hemorrhage of grade 3 to 4 specifically. The rates of infant death, transient tachypnea in the newborn, respiratory distress syndrome, bronchopulmonary dysplasia, need for ventilatory support, retinopathy of prematurity, and patent ductus arteriosus were slightly but not significantly lower in the progesterone group. Of the 17 neonatal deaths, 16 were due to complications of prematurity and 1 to intrapartum hypoxia subsequent to uterine rupture.

Nine of the infants were found to have congenital malformations (2.0 percent in each group). There was no consistent pattern to these defects, and none involved genital organs. One infant of a woman in the progesterone group had torsion of the testicles in utero, with subsequent infarction.

DISCUSSION

Treatment with 17P on a weekly basis, beginning at 16 to 20 weeks of gestation and continued to delivery or 36 weeks of gestation, significantly reduced the rate of preterm delivery before 37 weeks, 35 weeks, and 32 weeks of gestation among women at high risk for preterm delivery. The rates of several complications of prematurity were correspondingly decreased among the infants of women assigned to this therapy.

The women enrolled in this study had high rates of preterm delivery, with more than 50 percent of the women who received the placebo injections delivering before 37 weeks of gestation. This high rate of preterm delivery is most likely related to the history of previous preterm deliveries. The earlier in a pregnancy a preterm delivery occurs, the greater the chance of preterm delivery in a subsequent pregnancy.¹² In our study, the mean duration of gestation at the time of the qualifying delivery was 31 weeks, and a third of the women enrolled had had more than one previous preterm delivery. Therefore, the women in this study had particularly high risk. They were also strongly motivated, and compliance was excellent.

Preterm delivery has multiple causes.¹⁶ Some evidence suggests that the causes of early preterm

Table 2. Outcomes of Pregnancy According to Treatment Assignment.*

Outcome	Progesterone Group (N=306)	Placebo Group (N=153)	Relative Risk (95% CI)
	<i>no. (%)</i>		
Delivery before 37 wk of gestation	111 (36.3)	84 (54.9)	0.66 (0.54–0.81)
Spontaneous	90 (29.4)	69 (45.1)	0.65 (0.51–0.83)
Indicated because of complications	21 (6.9)	15 (9.8)	0.70 (0.37–1.32)
Black women	64 (35.4)	47 (52.2)	0.68 (0.51–0.90)
Nonblack women	47 (37.6)	37 (58.7)	0.64 (0.47–0.87)
Delivery before 35 wk of gestation	63 (20.6)	47 (30.7)	0.67 (0.48–0.93)
Delivery before 32 wk of gestation	35 (11.4)	30 (19.6)	0.58 (0.37–0.91)
Miscarriage at <20 wk of gestation	5 (1.6)	0	NA
Hospital visit for preterm labor	49 (16.0)	21 (13.8)	1.15 (0.72–1.86)
Tocolytic therapy	53 (17.3)	24 (15.9)	1.09 (0.70–1.69)
Corticosteroids for fetal lung maturity	52 (17.8)	30 (19.7)	0.91 (0.60–1.35)
Cesarean delivery	77 (25.2)	41 (26.8)	0.94 (0.68–1.30)
Chorioamnionitis	11 (3.6)	5 (3.3)	1.09 (0.39–3.09)

* Data on hospital visit for preterm labor were missing for 1 woman in the placebo group; data on tocolytic therapy were missing for 2 women in the placebo group; and data on corticosteroids for fetal lung maturity were missing for 14 women in the progesterone group and 1 woman in the placebo group. CI denotes confidence interval, and NA not applicable.

delivery differ from those of later preterm delivery, with earlier preterm deliveries more often being related to infection.¹⁷ Whereas 17P would not be expected to affect an infectious process, in this study, it provided potent protection against early as well as later preterm delivery. The mechanisms of action of 17P in prolonging gestation are not entirely known. The actions of progesterone on the pregnant myometrium include relaxation of myometrial smooth muscle, blocking of the action of oxytocin, and inhibition of the formation of gap junctions.^{18,19} In sheep, goats, and some other mammals, a decrease in plasma progesterone and an increase in circulating estrogen precede the onset of labor.²⁰ Although no such alteration in the ratio of plasma estrogen to progesterone precedes the onset of labor in primates, there is evidence that local changes in the progesterone level or the ratio of progesterone to estrogen in the placenta, decidua, or fetal membranes may be important in the ini-

Table 3. Fetal and Neonatal Outcomes According to Maternal Treatment Assignment.*

Outcome	Progesterone Group (N=306)	Placebo Group (N=153)	Relative Risk (95% CI)
	<i>no./total no. with data (%)</i>		
Fetal death, antepartum or intrapartum	6/306 (2.0)	2/153 (1.3)	1.50 (0.31–7.34)
Birth weight <2500 g	82/301 (27.2)	62/151 (41.1)	0.66 (0.51–0.87)
<1500 g	26/301 (8.6)	21/151 (13.9)	0.62 (0.36–1.07)
Neonatal death	8/306 (2.6)	9/153 (5.9)	0.44 (0.17–1.13)
Transient tachypnea	11/305 (3.6)	11/152 (7.2)	0.50 (0.22–1.12)
Respiratory distress syndrome	29/305 (9.5)	23/152 (15.1)	0.63 (0.38–1.05)
Bronchopulmonary dysplasia	4/305 (1.3)	5/152 (3.3)	0.40 (0.11–1.46)
Ventilatory support	26/303 (8.6)	22/151 (14.6)	0.59 (0.35–1.00)
Supplemental oxygen	45/303 (14.9)	36/151 (23.8)	0.62 (0.42–0.92)
Intraventricular hemorrhage			
Grade 3 or 4	2/305 (0.7)	0/153	NA
Any grade	4/305 (1.3)	8/153 (5.2)	0.25 (0.8–0.82)
Necrotizing enterocolitis	0/305	4/152 (2.6)	NA
Patent ductus arteriosus	7/305 (2.3)	8/151 (5.3)	0.43 (0.16–1.17)
Retinopathy	5/305 (1.6)	5/152 (3.3)	0.50 (0.15–1.70)
Proven sepsis	9/305 (3.0)	4/152 (2.6)	1.12 (0.35–3.58)

* Transient tachypnea was defined by a birth weight of less than 1000 g and a requirement for oxygen therapy, mechanical ventilation, or both during the first 24 hours of life in an infant in whom there was no evidence of other causes of respiratory distress. Respiratory distress syndrome was defined by a clinical diagnosis of type I respiratory distress syndrome and a requirement for oxygen therapy for at least 24 hours or by death before 24 hours in an infant who had received such a diagnosis and such therapy. Bronchopulmonary dysplasia was defined by a requirement for oxygen therapy (fraction of inspired oxygen, >0.21) for the first 28 days of life. Intraventricular hemorrhage was graded according to the most severe radiologic finding before hospital discharge. Necrotizing enterocolitis was defined by the unequivocal presence of intramural air on abdominal radiography, perforation seen on radiography, or stricture formation after an episode of suspected necrotizing enterocolitis. Infants were recorded as having patent ductus arteriosus if treatment for patent ductus arteriosus was documented in the medical records. Retinopathy was diagnosed by ophthalmologic examination. Proven sepsis was defined by positive cultures of blood, cerebrospinal fluid, or urine on admission to the nursery or (in the absence of positive cultures) clinical evidence of cardiovascular collapse or an unequivocal radiograph confirming the presence of infection in an infant with a clinical diagnosis of sepsis. CI denotes confidence interval, and NA not applicable.

tiation of labor in humans.²¹ In addition, administration of progesterone antagonists in women at term results in an increased rate of spontaneous labor.²²

We chose to use 17P because of reports of its effectiveness in some previous trials.^{4–6} Other stud-

ies showed no benefit, including a trial involving women with twin gestations⁸ and a trial in women with a low risk of preterm delivery.⁹ Most reported trials of other progesterone compounds have not demonstrated effectiveness in reducing the risk of preterm delivery.^{23–27} However, a recently reported trial in which progesterone suppositories were used suggested that this route of administration may be a viable alternative.²⁸ The risk of preterm delivery was lower among participants in that study than among the women in our study. The entry criteria included a history of delivery before 37 weeks of gestation, cervical cerclage, or a uterine malformation. The women in the placebo group in that trial had a rate of preterm delivery of 28.5 percent as compared with 13.8 percent in the progesterone group. These results lend support to the concept of prophylactic use of progesterone to prevent preterm delivery.

Treatment with 17P also resulted in improved neonatal outcomes. Although the reduction in neonatal mortality in the progesterone group was not significant (relative risk, 0.44; P=0.08), the trial was not designed with sufficient power to address this end point adequately. There were significant reductions in the rates of necrotizing enterocolitis, any intraventricular hemorrhage, and the need for supplemental oxygen in the progesterone group.

17P appeared to be safe. There was no increase in the rate of congenital anomalies in the progesterone group. These results are consistent with surveys of the literature that have indicated an absence of teratogenic effects from the use of 17P during pregnancy.^{29,30}

The results of our trial should be interpreted with caution. Although 17P proved to be effective in preventing preterm delivery in our cohort of women at very high risk, it may not be effective in women with a lower risk of preterm delivery,⁹ and most preterm deliveries occur in women with no previous preterm delivery. Therefore, our results may not be generalizable to women whose risk factors for preterm delivery are different from those of the women in this trial. In addition, although 17P significantly reduced the rate of preterm delivery among the women who received it, the rate of preterm delivery in this group remained very high (36.3 percent). Thus, the identification of other causes of preterm delivery and other methods of preventing it remains a pressing need.

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APPENDIX

Other members of the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network are as follows: University of Alabama, Birmingham: A. Northen, D. Rouse; Brown University: H. Silver, J. Tillinghast; Case Western Reserve University: P. Catalano, C. Milluzzi; University of Chicago: P. Jones, M. Lindheimer; University of Cincinnati: N. Elder, T. Siddiqi; Columbia University: M. D'Alton, V. Pembedton; George Washington University Biostatistics Center: A. Das, S. Leindecker; Magee Women's Hospital: M. Cotroneo, K. Lain; University of Miami: C. Alfonso, S. Beydoun; National Institute of Child Health and Human Development: D. McNellis, S. Pagliaro, A. Willoughby; University of North Carolina, Chapel Hill: K. Dorman, K. Moise; Northwestern University: G. Mallet, M. Socol; Ohio State University: F. Johnson, M. Landon; University of Tennessee: R. Ramsey; University of Texas at San Antonio: O. Langer, S. Nicholson; University of Texas at Houston: M. C. Day, L. Gilstrap; University of Texas Southwestern Medical Center: J. McCampbell, G. Wendel; MCP Hahnemann University: M. DiVito, J. Tolosa; University of Utah: M. Belfort, E. Taggart; Wake Forest University: E. Mueller-Heubach, M. Swain; Wayne State University: G. Norman, Y. Sorokin.

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