

ANTENATAL THYROTROPIN-RELEASING HORMONE TO PREVENT LUNG DISEASE IN PRETERM INFANTS

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ABSTRACT

Background Pulmonary disease is common in preterm infants, despite antenatal glucocorticoid therapy. The addition of antenatal thyrotropin-releasing hormone therapy has been reported to decrease pulmonary morbidity in these infants.

Methods We enrolled 996 women at 13 North American centers who were in preterm labor at <30 weeks' gestation in a double-blind, placebo-controlled, randomized trial of antenatal thyrotropin-releasing hormone, given intravenously in four doses of 400 µg each at eight-hour intervals. The primary outcome was chronic lung disease or death of the infant on or before the 28th day after delivery, and secondary outcomes were respiratory distress syndrome and chronic lung disease or death at 36 weeks' postmenstrual age. Complete data were available for 981 women and their 1134 live-born infants. The 769 infants born at ≤32 weeks' gestation were defined as the group at risk.

Results There were no significant differences between the at-risk treatment and placebo groups in mean (±SD) birth weight (1109±354 vs. 1097±355 g), gestational age (27.9±2.1 vs. 27.9±2.1 weeks), sex, or race. The frequencies of respiratory distress syndrome (66 percent vs. 65 percent), death at 28 days (11 percent vs. 11 percent), chronic lung disease or death at 28 days (45 percent vs. 42 percent) and at 36 weeks (32 percent vs. 34 percent), and other neonatal complications as well as the severity of lung disease were not significantly different in the at-risk treatment and placebo groups. Similarly, there were no differences in outcome between the treatment and placebo groups for the infants born at >32 weeks' gestation.

Conclusions In preterm infants at risk for lung disease, antenatal administration of thyrotropin-releasing hormone and glucocorticoid is no more beneficial than glucocorticoid alone. (N Engl J Med 1998; 338:493-8.)

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INFANTS born prematurely, particularly those delivered at ≤32 weeks' gestation, have immature lungs and a high incidence of respiratory distress syndrome and continuing chronic lung disease, also known as bronchopulmonary dysplasia. Lung disease remains the principal cause of mortality and morbidity in premature infants¹ despite the routine use of antenatal glucocorticoid therapy to increase lung maturity,²⁻⁶ surfactant-replacement therapy, and improved techniques of assisted ventilation.

Thyroid hormones stimulate fetal lung development in vitro and in animals,^{7,8} and the combination of thyroid hormone and glucocorticoid has synergistic effects.⁹⁻¹⁷ In humans, little thyroid hormone is transferred from mother to fetus, whereas fetal serum concentrations of thyroid hormone are increased by the administration of thyrotropin-releasing hormone to the mother. This hormone does cross the placenta and stimulates fetal secretion of thyrotropin, triiodothyronine, thyroxine, and prolactin.¹⁸⁻²¹

Antenatal glucocorticoid therapy reduces the incidence and severity of respiratory distress syndrome in premature infants but has no effect on the occurrence of chronic lung disease.^{4,6} In most but not all trials of antenatal thyrotropin-releasing hormone in combination with glucocorticoid, the incidence and severity of respiratory distress syndrome, chronic lung disease, or an adverse outcome, defined as chronic lung disease or death by 28 days' postnatal age, were reduced.²²⁻²⁷ However, one study was unblinded, most of the trials were relatively small, and most infants were not treated with surfactant. We undertook this randomized, double-blind, placebo-controlled trial to determine the efficacy and safety of antenatal

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thyrotropin-releasing hormone in combination with glucocorticoid in infants born to women who had preterm labor at <30 weeks' gestation. Surfactant was administered when clinically indicated.

METHODS

Patient Enrollment and Evaluation

Women in active labor with gestations of at least 24 but less than 30 weeks were recruited at 13 North American centers between October 1992 and December 1996. Women who had bleeding, infection, hypertension (blood pressure, >140/90 mm Hg), fetuses with hydrops or life-threatening anomalies, or one dead fetus in multiple pregnancies were not eligible for the study. The study protocol was approved by the institutional review board at each center, and informed consent was obtained from all the women.

The women were randomly assigned within centers to the treatment or placebo group in permuted blocks of four. The study was double-blinded, and only the pharmacies at the participating centers had the randomization schedule. The women were each given four doses of 400 μ g of thyrotropin-releasing hormone (Thyponine, Abbott Laboratories, Abbott Park, Ill., or Thyrel, Ferring Laboratories, Tarrytown, N.Y.) intravenously in 50 ml of normal saline or were given normal saline alone over a period of 20 minutes at 8-hour intervals. All the women received two 12-mg doses of intramuscular betamethasone 24 hours apart, or four 6-mg doses of intramuscular dexamethasone at 12-hour intervals, starting within 72 hours of the time of the first dose of thyrotropin-releasing hormone. According to the trial design, only one course of thyrotropin-releasing hormone was given; however, additional courses of glucocorticoid and tocolytic-drug therapy were given at the discretion of the physician. Tocolytic drugs were given to 85 percent of the women in the treatment group and 83 percent of the women in the placebo group, and there were no differences between the two groups in the use of β -adrenergic agonists (mean for both groups, 57 percent), magnesium sulfate (70 percent), prostaglandin-synthesis inhibitors (24 percent), or calcium-channel blockers (9 percent).

The women's pulse rates and blood pressures were monitored closely during and after the infusions, and assessments were made for indications of fetal distress. Gestational age was assigned at the time of the mother's enrollment on the basis of an ultrasound examination, if performed at less than 20 weeks' gestation, and on the basis of menstrual dates if appropriate ultrasound results were not available.

In accordance with the protocol, infants weighing \leq 800 g were treated at birth with surfactant (Exosurf, Glaxo Wellcome, Research Triangle Park, N.C., or Survant, Abbott Laboratories), and those weighing more than 800 g were treated after birth (rescue treatment) with surfactant as needed for respiratory distress. The infants received standard neonatal intensive care at the discretion of their physicians. Respiratory distress syndrome was defined as the need for oxygen and either the need for assisted ventilation for more than 48 hours after birth or radiologic findings consistent with respiratory distress syndrome.

The primary outcome was infant death on or before the 28th day after delivery or chronic lung disease, defined as the need for oxygen therapy for 21 of the first 28 days of life, including day 28. These end points were evaluated both for the entire group of infants and for the group of infants who were born at \leq 32 weeks' gestation (defined as the group at risk for lung disease).

Secondary outcome measures were the incidence of chronic lung disease or death at \leq 36 weeks' postmenstrual age (an age at which most infants should be ready for discharge home), calculated from the first day of the last menstrual period, and the occurrence of other complications of prematurity, including patent ductus arteriosus, necrotizing enterocolitis, intraventricular hemorrhage, and retinopathy of prematurity.

Cord-blood samples were obtained at nine centers to deter-

mine the fetal response to thyrotropin-releasing hormone. Plasma thyrotropin and triiodothyronine were measured by immunoassay (Nichols Institute, San Juan Capistrano, Calif.) in those samples.

Statistical Analysis

A sample consisting of 1090 live births was required to detect a decrease of 40 percent in the incidence of chronic lung disease in the group treated with thyrotropin-releasing hormone as compared with the placebo group, with 80 percent power, allowing for two interim analyses.²⁸ The stopping boundaries were not crossed at the time of these two analyses, and therefore the study was completed.

The characteristics of the mothers and infants and the outcomes in the two groups were compared with the use of Fisher's exact test or its extension to tables larger than two-by-two tables. Continuous characteristics, such as gestational age and birth weight, were compared with the use of Student's t-test.

Odds ratios and confidence intervals were calculated for all outcomes of the group at risk and the group not at risk. The infants who died before reaching 28 days of life or 36 weeks' postmenstrual age were considered to have chronic lung disease in between-group comparisons. Secondary analysis in the group at risk examined outcomes according to gestational age and other complications seen in the preterm infant.

All analyses were based on the intention-to-treat principle, and all statistical tests were two-sided.

RESULTS

Between October 1992 and December 1996, 2209 women were screened, of whom 1516 (69 percent) were eligible for the study; 996 of those eligible (66 percent) were enrolled. Complete data were available for 981 of these women and their 1134 live-born infants. There were no significant differences in age, race, marital status, prenatal care, or pregnancy history between the mothers in the two groups, nor were there differences in their fetuses' mean (\pm SD) gestational ages at the time of randomization (Table 1).

There were the expected maternal side effects of administering thyrotropin-releasing hormone. The incidence of nausea and vomiting was higher in the treatment group than in the placebo group (11 percent vs. 2 percent, $P < 0.001$), as were the incidences of flushing (29 percent vs. 11 percent, $P < 0.001$) and headache (5 percent vs. 1 percent, $P < 0.001$). These symptoms were transient and often did not recur with subsequent doses of thyrotropin-releasing hormone. Eighteen women in the treatment group (3.7 percent) and seven in the placebo group (1.4 percent, $P = 0.01$) withdrew from the trial because of side effects. There were no reported increases in maternal blood pressures or pulse rates, and no fetal side effects were noted during the infusions.

There were 11 stillbirths and 1134 live births, with 844 singleton and 290 multiple births. Seven hundred sixty-nine (68 percent) of the infants were born at \leq 32 weeks and were considered the at-risk group. There were no significant differences between the treatment and placebo groups in the incidence of respiratory distress syndrome, death, or chronic lung disease 28 days after delivery or at 36 postmenstrual weeks in either the group at risk or

the group not at risk (Table 2). There were also no significant differences in these outcomes between treatment and placebo groups consisting of singleton infants and singleton infants plus one randomly selected infant from each mother with multiple births.

In two previous trials, thyrotropin-releasing hormone was beneficial in infants born between 24 hours and 10 days after administration to the mothers.^{23,25} We therefore examined the outcomes for all infants born less than 24 hours after administration, 24 hours to 10 days after administration, and more than 10 days after administration. There were no significant differences between the two groups at any of these times (Table 3).

The incidence of chronic lung disease or death in infants 28 days after delivery and at 36 weeks' post-menstrual age decreased with increasing gestational age in the at-risk group (Table 4). There were no differences between the two groups in the incidence of chronic lung disease or death according to the type of birth (singleton or multiple), sex, race, or the need for treatment with surfactant (Table 5). Although the outcomes for the two groups were not different at any of the individual centers (data not shown), there was wide variation between the centers in the overall incidence of chronic lung disease or death in the infants at risk (ranges, 18 to 63 percent at 28 days and 25 to 41 percent at 36 weeks).

Cord blood was available from 21 infants born within six hours after the mothers had received thyrotropin-releasing hormone (12 women) or placebo (9 women). The infants of these mothers had similar gestational ages (mean [\pm SD], 27.1 \pm 1.5 weeks in the treatment group vs. 26.2 \pm 1.6 weeks in the placebo group) and birth weights (1051 \pm 213 g vs. 911 \pm 265 g). The mean plasma thyrotropin concentrations were 20.0 \pm 16.6 and 4.3 \pm 2.1 μ U per milliliter ($P=0.01$), and the mean serum triiodothyronine concentrations were 81 \pm 44 ng per deciliter (1.2 \pm 0.7 nmol per liter) and 56 \pm 26 ng per deciliter (0.9 \pm 0.4 nmol per liter) in the treatment and placebo groups, respectively.

DISCUSSION

This trial was undertaken in 1992 to assess the efficacy and safety of antenatal administration of thyrotropin-releasing hormone to improve pulmonary outcomes in preterm infants. Thyrotropin-releasing hormone appeared to be beneficial in all previous studies²²⁻²⁵ except an Australian trial²⁷ in which a lower dose (200 μ g, as opposed to 400 μ g) and different schedule (every 12 hours, as opposed to every 8 hours) were used. Changes in neonatal care during the past decade, in particular the routine use of surfactant, and improved survival of very-low-birth-weight infants also contributed to the rationale for conducting this trial. Finally, findings of low plasma

TABLE 1. BASE-LINE CHARACTERISTICS OF MOTHERS AND INFANTS IN THE THYROTROPIN-RELEASING HORMONE (TRH) AND PLACEBO GROUPS.*

CHARACTERISTIC	TRH	PLACEBO
Mothers		
No.	486	495
Age — yr	28 \pm 8	28 \pm 7
Race or ethnic group — no. (%)		
White	230 (47)	238 (48)
Black	114 (23)	111 (22)
Hispanic	107 (22)	107 (22)
Other or unknown	35 (7)	39 (8)
Received all infusions — no. (%)	391 (80)	422 (85)
Singleton pregnancy — no. (%)	414 (85)	430 (87)
Infants at risk for lung disease†		
No.	392	377
Mode of delivery — no. (%)		
Vaginal	204 (52)	188 (50)
Cesarean	188 (48)	183 (49)
Unknown	0	6 (2)
Sex — no. (%)		
Male	230 (59)	198 (53)
Female	162 (41)	179 (47)
Race or ethnic group — no. (%)		
White	194 (49)	190 (50)
Black	89 (23)	74 (20)
Hispanic	83 (21)	81 (21)
Other and unknown	26 (7)	32 (8)
Gestational age — wk	27.9 \pm 2.1	27.9 \pm 2.1
Birth weight — g	1109 \pm 354	1097 \pm 355
Infants not at risk for lung disease‡		
No.	171	194
Mode of delivery — no. (%)		
Vaginal	111 (65)	117 (60)
Cesarean	58 (34)	71 (37)
Unknown	2 (1)	6 (3)
Sex — no. (%)		
Male	93 (54)	97 (50)
Female	78 (46)	97 (50)
Race or ethnic group — no. (%)		
White	89 (52)	87 (45)
Black	41 (24)	53 (27)
Hispanic	30 (18)	40 (21)
Other or unknown	11 (6)	14 (7)
Gestational age — wk	36.4 \pm 2.4	36.0 \pm 2.5
Birth weight — g	2659 \pm 641	2535 \pm 677

*Plus-minus values are means \pm SD.

†Infants at risk for lung disease were born at \leq 32 weeks' gestation.

‡Infants not at risk for lung disease were born at $>$ 32 weeks' gestation.

concentrations of thyroid hormone at birth in a subgroup of infants treated with thyrotropin-releasing hormone²¹ aroused concern about possible effects on the function of the hypothalamic-pituitary-thyroid axis after birth.

In our study, antenatal administration of thyrotropin-releasing hormone had no effect on pulmonary outcomes in either the group of infants who were delivered at \leq 32 weeks or those considered not at risk (delivered at $>$ 32 weeks). The incidences of respiratory distress syndrome and chronic lung disease decreased with advancing gestational age in both the treatment and placebo groups, in a manner consistent with the recognized role of lung immaturity in

TABLE 2. OUTCOMES OF INFANTS IN THE THYROTROPIN-RELEASING HORMONE (TRH) AND PLACEBO GROUPS.*

OUTCOME	INFANTS AT RISK FOR LUNG DISEASE†			INFANTS NOT AT RISK FOR LUNG DISEASE‡		
	TRH (N=392)	PLACEBO (N=377)	ODDS RATIO (95% CI)	TRH (N=171)	PLACEBO (N=194)	ODDS RATIO (95% CI)
	no. (%)			no. (%)		
Respiratory distress syndrome	260 (66)	244 (65)	1.1 (0.8–1.5)	5 (3)	13 (7)	0.4 (0.1–1.3)
Death ≤28 days after delivery	43 (11)	42 (11)	1.0 (0.6–1.6)	2 (1)	1 (1)	2.3 (0.1–135)
Chronic lung disease or death ≤28 days after delivery	175 (45)	157 (42)	1.1 (0.8–1.5)	3 (2)	2 (1)	1.7 (0.2–20.7)
Death between 29 days after delivery and 36 wk postmenstrual age	3 (1)	4 (1)	0.7 (0.1–4.3)	NA	NA	—
Chronic lung disease or death at ≤36 wk postmenstrual age	125 (32)	128 (34)	0.9 (0.7–1.3)	3 (2)	2 (1)	1.7 (0.2–20.7)
Death at >36 wk postmenstrual age	4 (1)	4 (1)	1.0 (0.2–5.2)	2 (1)	2 (1)	1.1 (0.1–15.8)
Total deaths	50 (13)	50 (13)	1.0 (0.6–1.5)	4 (2)	2 (1)	2.3 (0.3–25.7)
Pressor drug given during first week of life	112 (29)	105 (28)	1.0 (0.8–1.4)	2 (1)	2 (1)	1.1 (0.1–15.8)
Air leak	31 (8)	29 (8)	1.0 (0.6–1.8)	1 (1)	1 (1)	1.1 (0.0–89.6)
Glucocorticoid given for chronic lung disease	130 (33)	136 (36)	0.9 (0.7–1.2)	1 (1)	1 (1)	1.1 (0.0–89.6)
Patent ductus arteriosus treated with indomethacin or surgery	100 (26)	102 (27)	0.9 (0.7–1.3)	0	0	—
Intraventricular hemorrhage						
Any	123 (31)	115 (31)	1.0 (0.8–1.4)	1 (1)	2 (1)	0.6 (0.0–11.0)
Grade 3 or 4	38 (10)	31 (8)	1.2 (0.7–2.0)	0	1 (1)	—
Necrotizing enterocolitis						
Any	16 (4)	18 (5)	0.9 (0.4–1.8)	3 (2)	0	—
Requiring surgery	11 (3)	7 (2)	1.5 (0.5–4.7)	0	0	—
Retinopathy of prematurity						
Any	122 (31)	144 (38)	0.7 (0.5–1.0)	0	0	—
Stage 3 or 4	32 (8)	30 (8)	1.0 (0.6–1.8)	0	0	—

*CI denotes confidence interval, and NA not available.

†Infants at risk for lung disease were born at ≤32 weeks' gestation.

‡Infants not at risk for lung disease were born at >32 weeks' gestation.

the pathogenesis of these disorders. There was no indication that thyrotropin-releasing hormone improved pulmonary outcome in any subgroup of infants defined by gestational age or treatment interval. There was also no evidence of either beneficial or adverse effects of thyrotropin-releasing hormone on the occurrence of patent ductus arteriosus, necrotizing enterocolitis, intraventricular hemorrhage, or retinopathy of prematurity. The wide ranges in the incidence of both chronic lung disease and death at the various centers, without apparent benefit from thyrotropin-releasing hormone, could be due to differences among the centers in the ethnic composition of the study groups, the severity of the initial illness, or clinical practices.

We did find that administration of thyrotropin-releasing hormone had the expected transient side effects of nausea and vomiting, headache, and flushing in the mother, but the majority of women had no side effects. These side effects usually did not recur with subsequent infusions, and few women with-

drew from the study even after having one of these problems. Virtually all the women were receiving at least one tocolytic drug each, but there was no difference in outcome based on the type of tocolytic drug given.

Our finding that thyrotropin-releasing hormone did not lessen respiratory morbidity in premature infants agrees with the results of the Australian Collaborative Trial of Antenatal Thyrotropin-Releasing Hormone²⁷ and a recent study by Maturana et al.²⁹ A comparison of these three negative trials and the four earlier trials suggesting efficacy reveals several differences. The earlier trials involved smaller numbers of women with fewer infants in the group at risk, one trial was not blinded,²² and one was published only as an abstract.²⁴ These limitations may have produced inaccurate conclusions. It is also possible, however, that changes in the management of preterm birth during the past five years, particularly more aggressive respiratory care, and improved survival of infants with less than 26 weeks' gestation

TABLE 3. OUTCOME ACCORDING TO THE TIME OF THE LAST INFUSION FOR ALL INFANTS IN THE THYROTROPIN-RELEASING HORMONE (TRH) AND PLACEBO GROUPS.*

OUTCOME	INFUSION <24 HR BEFORE DELIVERY		INFUSION 24 HR–10 DAYS BEFORE DELIVERY		INFUSION >10 DAYS BEFORE DELIVERY	
	TRH (N=108)	PLACEBO (N=104)	TRH (N=169)	PLACEBO (N=164)	TRH (N=270)	PLACEBO (N=286)
	number (percent)					
Respiratory distress syndrome	81 (75)	83 (80)	111 (66)	112 (68)	63 (23)	55 (19)
Chronic lung disease or death ≤28 days after delivery	60 (56)	60 (58)	72 (43)	67 (41)	39 (14)	28 (10)
Chronic lung disease or death at ≤36 wk postmenstrual age	45 (42)	45 (43)	45 (27)	51 (31)	33 (12)	29 (10)

*The time of the last infusion was not available for 33 infants.

TABLE 4. OUTCOME ACCORDING TO GESTATIONAL AGE IN THE AT-RISK INFANTS IN THE THYROTROPIN-RELEASING HORMONE (TRH) AND PLACEBO GROUPS.*

OUTCOME	>24–26 Wk		>26–28 Wk		>28–30 Wk		>30–32 Wk	
	TRH (N=90)	PLACEBO (N=94)	TRH (N=118)	PLACEBO (N=107)	TRH (N=114)	PLACEBO (N=117)	TRH (N=70)	PLACEBO (N=59)
Birth weight — g	748±146	755±112	984±170	963±190	1239±217	1261±246	1572±332	1555±342
Respiratory distress syndrome — no. (%)	82 (91)	81 (86)	90 (76)	85 (79)	62 (54)	58 (50)	26 (37)	20 (34)
Chronic lung disease or death ≤28 days after delivery — no. (%)	75 (83)	73 (78)	61 (52)	56 (52)	32 (28)	21 (18)	7 (10)	7 (12)
Death at ≤36 wk postmenstrual age — no. (%)	31 (34)	30 (32)	10 (8)	11 (10)	5 (4)	5 (4)	0	0
Chronic lung disease or death at ≤36 wk postmenstrual age — no. (%)	55 (61)	62 (66)	36 (31)	36 (34)	24 (21)	23 (20)	10 (14)	7 (12)
Surfactant given — no. (%)	78 (87)	73 (78)	76 (64)	64 (60)	46 (40)	44 (38)	17 (24)	21 (36)

*Plus-minus values are means ±SD.

have influenced the response to thyrotropin-releasing hormone. In very small infants, immaturity of the lungs may have a more dominant role in the disease process than surfactant deficiency, and therefore these infants could be less responsive to thyrotropin-releasing hormone. We also found no evidence that antenatal thyrotropin-releasing hormone decreased the need for surfactant. In contrast to the earlier trials, which enrolled women with gestations of ≤32 weeks, we enrolled only women with gestations of less than 30 weeks. If thyrotropin-releasing hormone is effective primarily in more mature fetuses, delivered within 10 days after treatment, this benefit might have been missed in our study.

The plasma concentrations of thyrotropin and triiodothyronine at birth in infants delivered less than six hours after the last dose of thyrotropin-releasing hormone or placebo were similar to those in another study of somewhat older infants.²¹ This suggests that the lack of efficacy of thyrotropin-releasing hormone in this trial did not result from reduced placental transfer of the hormone or from unresponsiveness of the fetal pituitary–thyroid axis.

TABLE 5. OCCURRENCE OF CHRONIC LUNG DISEASE ACCORDING TO MULTIPLICITY OF BIRTHS, RACE, SEX, AND SURFACTANT REQUIREMENT IN THE INFANTS AT RISK IN THE THYROTROPIN-RELEASING HORMONE (TRH) AND PLACEBO GROUPS.*

CHARACTERISTIC	CHRONIC LUNG DISEASE OR DEATH ≤28 DAYS AFTER DELIVERY		CHRONIC LUNG DISEASE OR DEATH AT ≤36 WK POSTMENSTRUAL AGE	
	TRH	PLACEBO	TRH	PLACEBO
	number (percent)			
Singleton birth	129 (44)	120 (42)	91 (31)	89 (31)
Multiple birth	46 (45)	37 (40)	34 (33)	39 (42)
Male sex	106 (45)	81 (42)	80 (35)	67 (34)
Race or ethnic group				
White	86 (44)	86 (46)	64 (33)	74 (39)
Black	38 (42)	26 (35)	30 (34)	20 (27)
Hispanic	40 (48)	30 (37)	27 (33)	26 (32)
Other or unknown	7 (39)	8 (36)	3 (15)	5 (23)
Surfactant given	135 (62)	118 (58)	105 (47)	98 (48)

*Infants at risk for lung disease were born at ≤32 weeks' gestation. The total number of infants with each characteristic is given in Table 1, except for singleton and multiple births. The number of singleton births in the TRH group was 290, and in the placebo group it was 284. The number of multiple births in the TRH group was 102, and in the placebo group it was 93.

Since the earlier reports, thyrotropin-releasing hormone has been used in a number of centers throughout the United States on the assumption that it was both effective and safe. Although it does appear safe, we found no evidence of efficacy. Furthermore, initial follow-up data from the Australian trial^{30,31} suggest that antenatal thyrotropin-releasing hormone may be associated with delays in early developmental milestones. We conclude that antenatal administration of thyrotropin-releasing hormone is not indicated for women who are at risk for delivering a premature infant.

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APPENDIX

In addition to the authors, the following members of the North American Thyrotropin-Releasing Hormone Study Group participated in this study: B. Planer, B. Banks, M. McCarthy, and E. Escobar, Children's Hospital of Philadelphia, Philadelphia; M. Morgan, E. Anday, K. Mooney, M. Johnson, and J. Merrill, Hospital of the University of Pennsylvania, Philadelphia; N. Newton and J. Milar, University of California, San Francisco, Medical Center, San Francisco; M. Ross, D. Polk, and S. Harrington, Harbor-UCLA Medical Center, Torrance, Calif.; K. Ash and J. Frank, Ottawa General Hospital, Ottawa, Ont., Canada; E. Tyrala and L. Chan, Temple University Hospital, Philadelphia; J. Lioy and R. Librizzi, West Jersey Hospital, Voorhees, N.J.; J. Garbaciak and E. Ramthun, St. Joseph's Hospital, Phoenix, Ariz.; C. Carballo, Good Samaritan Hospital, Phoenix, Ariz.; T. Moore and E. Milan, University of California, San Diego, Medical Center, San Diego; H. Schneider and D. Block, Kaiser Permanente Medical Center, San Diego, Calif.; J. Keith and M. Rivera-Alsina, Naval Medical Center, San Diego, Calif.; N. Ragavan and N. Dunn, Abington Memorial Hospital, Philadelphia; V. Bhutani, S. Weiner, and M. Grous, Pennsylvania Hospital, Philadelphia. The members of the Data Safety and Monitoring Committee were M. Bracken, Yale University, New Haven, Conn.; R. Goldenberg, University of Alabama at Birmingham, Birmingham; R. Soll, University of Vermont, Burlington; and L. Wright, National Institute of Child Health and Human Development (ad hoc).

REFERENCES

- Zimmerman JJ, Farrell PM. Advances and issues in bronchopulmonary dysplasia. *Curr Probl Pediatr* 1994;24:159-70.
- Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics* 1972;50:515-25.
- Kari MA, Hallman M, Eronen M, et al. Prenatal dexamethasone treatment in conjunction with rescue therapy of human surfactant: a randomized placebo-controlled multicenter study. *Pediatrics* 1994;93:730-6.
- Crowley PA. Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994. *Am J Obstet Gynecol* 1995;173:322-35.
- Ballard PL, Ballard RA. Scientific basis and therapeutic regimens for use of antenatal glucocorticoids. *Am J Obstet Gynecol* 1995;173:254-62.
- NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. Effect of corticosteroids for fetal maturation on perinatal outcomes. *JAMA* 1995;273:413-8.
- Ballard PL, Hovey ML, Gonzales LK. Thyroid hormone stimulation of phosphatidylcholine synthesis in cultured fetal rabbit lung. *J Clin Invest* 1984;74:898-905.
- Thyroid hormones: effects and binding. In: Ballard PL. *Hormones and lung maturation*. Vol. 28 of Monographs on endocrinology. Berlin, Germany: Springer-Verlag, 1986:197-236.
- Gross I, Dynia DW, Wilson CM, Ingleson LD, Gewolb IH, Rooney SA. Glucocorticoid-thyroid hormone interactions in fetal rat lung. *Pediatr Res* 1984;18:191-6.
- Gonzales LW, Ballard PL, Ertsey R, Williams MC. Glucocorticoids and thyroid hormones stimulate biochemical and morphological differentiation of human fetal lung in organ culture. *J Clin Endocrinol Metab* 1986;62:678-91.
- Schellenberg JC, Liggins GC, Manzai M, Kitterman JA, Lee CCH. Synergistic hormonal effects on lung maturation in fetal sheep. *J Appl Physiol* 1988;65:94-100.
- Liggins GC, Schellenberg JC, Manzai M, Kitterman JA, Lee CCH. Synergism of cortisol and thyrotropin-releasing hormone on lung maturation in fetal sheep. *J Appl Physiol* 1988;65:1880-4.
- Warburton D, Parton L, Buckley S, Cosico L, Enns G, Saluna T. Combined effects of corticosteroid, thyroid hormones, and β -agonist on surfactant, pulmonary mechanics, and β -receptor binding in fetal lamb lung. *Pediatr Res* 1988;24:166-70.
- Boshier DP, Holloway H, Liggins GC, Marshall RJ. Morphometric analyses of the effects of thyrotropin releasing hormone and cortisol on the lungs of fetal sheep. *J Dev Physiol* 1989;12:49-54.
- Ikegami M, Jobe AH, Pettenazzo A, Seidner SR, Berry DD, Ruffini L. Effects of maternal treatment with corticosteroids, T3, TRH, and their combinations on lung function of ventilated preterm rabbits with and without surfactant treatments. *Am Rev Respir Dis* 1987;136:892-8.
- Ikegami M, Polk D, Tabor B, Lewis J, Yamada T, Jobe AH. Corticosteroid and thyrotropin-releasing hormone effects on preterm sheep lung function. *J Appl Physiol* 1991;70:2268-78.
- Moya FR, Gross I. Combined hormonal therapy for the prevention of respiratory distress syndrome and its consequences. *Semin Perinatol* 1993;17:267-74.
- Moya F, Mena P, Heusser F, et al. Response of the maternal, fetal, and neonatal pituitary-thyroid axis to thyrotropin-releasing hormone. *Pediatr Res* 1986;20:982-6.
- Moya F, Mena P, Foradori A, Becerra M, Inzunza A, Germain A. Effect of maternal administration of thyrotropin releasing hormone on the preterm fetal pituitary-thyroid axis. *J Pediatr* 1991;119:966-71.
- de Zegher F, Spitz B, Devlieger H. Prenatal treatment with thyrotropin releasing hormone to prevent neonatal respiratory distress. *Arch Dis Child* 1992;67:450-4.
- Ballard PL, Ballard RA, Creasy RK, et al. Plasma thyroid hormones and prolactin in premature infants and their mothers after prenatal treatment with thyrotropin-releasing hormone. *Pediatr Res* 1992;32:673-8.
- Morales WJ, O'Brien WE, Angel JL, Knuppel RA, Sawai S. Fetal lung maturation: the combined use of corticosteroids and thyrotropin-releasing hormone. *Obstet Gynecol* 1989;73:111-6.
- Ballard RA, Ballard PL, Creasy RK, et al. Respiratory disease in very-low-birthweight infants after prenatal thyrotropin-releasing hormone and glucocorticoid. *Lancet* 1992;339:510-5.
- Althabe F, Fustinana C, Althabe O, Ceriani Cernades JM. Controlled trial of prenatal betamethasone plus TRH vs. betamethasone plus placebo for prevention of RDS in preterm infants. *Pediatr Res* 1991;29:Suppl:200A. abstract.
- Knight DB, Liggins GC, Wealthall SR. A randomized, controlled trial of antepartum thyrotropin-releasing hormone and betamethasone in the prevention of respiratory disease in preterm infants. *Am J Obstet Gynecol* 1994;171:11-6.
- Crowther CA, Alfirevic Z. Antenatal thyrotropin-releasing hormone (TRH) prior to preterm delivery. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, eds. *Pregnancy and childbirth module*. Cochrane Database of Systematic Reviews, 1994. (Review no. 04749.)
- Australian Collaborative Trial of Antenatal Thyrotropin-Releasing Hormone (ACTOBAT) for prevention of neonatal respiratory disease. *Lancet* 1995;345:877-82.
- O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.
- Maturana A, Torres J, Salinas R, Moya F. Collaborative trial of prenatal thyrotropin-releasing hormone and corticosteroids for prevention of respiratory distress syndrome. *Am J Obstet Gynecol* 1998;178:33-9.
- Crowther CA, Hiller JE, Haslam RR, Robinson JS, ACTOBAT Study Group. Australian Collaborative Trial of Antenatal Thyrotropin-Releasing Hormone: adverse effects at 12-month follow-up. *Pediatrics* 1997;99:311-7.
- McCormick M. The credibility of the ACTOBAT follow-up study. *Pediatrics* 1997;99:476-8.