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Plasma Thyroid Hormones and Prolactin in Premature Infants and Their Mothers after Prenatal Treatment with Thyrotropin-Releasing Hormone

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ABSTRACT. We assayed TSH, triiodothyronine, free thyroxine, and prolactin (PRL) in plasma of women and infants participating in a trial of prenatal thyrotropin-releasing hormone (TRH) treatment for prevention of newborn lung disease. Women in labor at 26–34 wk of gestation received 400 μg of TRH i.v. every 8 h (one to four doses) plus 12 mg betamethasone (one or two doses); controls received saline plus betamethasone. Mean cord concentrations in control infants were TSH 9.7 mU/L, triiodothyronine 0.6 nmol/L (40.2 ng/dL), free thyroxine 14.4 pmol/L (1.13 ng/dL), and PRL 67.6 μg/L. TRH increased maternal plasma TSH by 100% at 2–4 h after treatment and decreased levels by 28–34% at 5–36 h. In cord blood of treated infants delivered at 2–6 h, TSH, triiodothyronine, and PRL were all increased about 2-fold *versus* control, and free thyroxine was increased 19%; the response was similar after one, two, three, or four doses of TRH. In treated infants delivered at 13–36 h, cord TSH and triiodothyronine levels were decreased 62 and 54%, respectively, and all thyroid hormones were lower after birth at 2 h of age *versus* control. We conclude that prenatal TRH administration increases thyroid hormones and PRL in preterm fetuses to levels similar to those normally occurring at term. Pituitary-thyroid function is transiently suppressed after treatment to a greater extent in fetus than mother, and infants born during the early phase of suppression do not have the normal postnatal surge in thyroid hormones. (*Pediatr Res* 32: 673–678, 1992)

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Abbreviations

RDS, respiratory distress syndrome
TRH, thyrotropin-releasing hormone
PRL, prolactin
T_3, triiodothyronine
T_4, thyroxine

Antenatal glucocorticoid therapy decreases the incidence of RDS and several other complications of preterm birth. Although this treatment is efficacious and safe, it does not always prevent RDS, and infants of very low birth weight often develop chronic lung disease. Recent efforts to improve the efficacy of prenatal preventive therapy have assessed effects of thyroid hormones.

Treatment with thyroid hormones has additive or synergistic effects with glucocorticoids in stimulating lung development in animals and cultured tissue, and endogenous T_3 appears to have a role in normal maturation (1–12). Earlier studies in humans used intraamniotic administration of T_3 or T_4 in an attempt to accelerate fetal lung maturation (13–14). More recently, clinical studies have used maternal treatment with TRH, a tripeptide that readily crosses the placenta (15–19). Although levels of thyroid hormones and PRL have been described for TRH-treated fetuses at term, there is relatively little information on hormone responses in premature infants.

A collaborative trial of prenatal administration of TRH plus glucocorticoid was carried out to determine whether this combined therapy would be more effective than glucocorticoid alone in reducing the incidence and severity of lung disease and other problems of the very low birth weight infant. The results of this trial, which were recently published (20), indicated that significantly fewer TRH-treated infants developed chronic lung disease (requirement for supplemental oxygen at 28 d of age or 36 wk postconception). In this article, we report our findings for plasma concentrations of thyroid hormones and PRL in women and infants who were enrolled in the collaborative trial. We describe the stimulation and subsequent suppression of thyroid function after TRH treatment. Preliminary findings have been previously reported (20, 21).

MATERIALS AND METHODS

Patient population. The plasma samples analyzed in this study were obtained from women and their infants enrolled in a

multicenter, blinded, randomized, placebo-controlled trial of prenatal TRH therapy (19). The TRH treatment group ($n = 99$) received 400 μg of TRH administered i.v. in 50 mL of saline during a 20-min infusion; unless delivery occurred, treatment was repeated at 8-h intervals for a total of four doses. In addition, the women received two doses of betamethasone (Celestone Soluspan, Schering Corp., Kenilworth, NJ) 12 mg intramuscularly given 12 h apart. The control group ($n = 105$) received 50 mL of normal saline (placebo) during a 20-min infusion, every 8 h for up to four doses, and betamethasone was administered on the same schedule as in the TRH group. The study was approved by human experimentation committees at each institution.

Assays. Samples of maternal venous, umbilical venous, and umbilical arterial blood were collected at delivery from patients who delivered ≤10 d after entry into the trial. In addition, blood samples were taken from an umbilical arterial catheter or peripheral vein from newborn infants at 2 h and approximately 24 h of age. Plasma was obtained by centrifugation and stored at −70°C.

RIA for TSH, T_3, free T_4, and PRL were performed in duplicate on the samples. When there was limited plasma volume, priority was given to assay of TSH and free T_4. The RIA kits for TSH, free T_4, and PRL were obtained from Becton Dickinson (Orangeburg, NY) and had sensitivity and interassay coefficient of variation values of 0.2 mU/L and 7.4%, 0.1 pmol/L and 4.5%, and 1 μg/L and 6.1%, respectively. The T_3 assay kit was purchased from Corning Medical (Medfield, MA) and had sensitivity and interassay coefficients of variation values of 0.1 nmol/L and 5.8%, respectively. The volume of all samples was adjusted to give results in the linear range of the assay. Repeated assays of selected samples indicated that there was no effect of storage time on the hormone concentrations. For individual cord umbilical samples, results for venous and arterial plasma were similar for each of the assays.

Data analysis. All of the assays and analyses were performed in a blinded fashion before the treatment code was broken. In the case of cord umbilical samples, the mean value for arterial and venous specimens was used in the final data analysis, which was limited to pregnancies of 26–34 wk of gestation in which delivery occurred within 10 d of the last dose of TRH. Results for the treated group were evaluated by the interval from the last dose of TRH to delivery (see Results), and data were compared with the control population. Based on the observed time course of hormone concentrations in individual infants, we used an initial interval after the last dose of TRH of 2–4 h for TSH and 2–6 h for T_3, free T_4, and PRL. The concentrations of hormones in the control samples did not vary with time from last dose of placebo (2 h to 10 d), and a mean value for the entire group was used in the comparisons. Mean ± SEM values are presented, and statistical comparisons were made using analysis of variance with Bonferroni adjustment for multiple comparisons, linear regression, and unpaired *t* tests.

RESULTS

Control group. We limited our analysis to control and treated infants of ≤34 wk gestation who delivered ≤10 d after entry into the trial and for whom blood samples were collected. The mean gestational age for control infants ($n = 62$) was 29.6 wk, and the distribution of infants by gestational age was comparable to the TRH-treated population ($n = 71$, mean 30.0 wk). There were no significant differences between control and treated infants for incidence of RDS, intracranial hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, or for Apgar scores.

The control women and their fetuses were all treated with betamethasone; however, there was no effect of the treatment interval (last dose to delivery) on maternal or cord hormone concentrations (data not shown), suggesting that corticosteroid therapy did not affect the concentration of thyroid hormones or PRL. Table 1 summarizes mean concentrations of hormones in maternal and infant plasma for the control group. The data are similar to previously described results and confirm differences in hormone concentrations between cord and maternal plasma as well as the postnatal surge in TSH and thyroid hormones (22). There was a significant positive correlation with gestational age for PRL between 26 and 34 wk ($r = 0.34$, $p < 0.001$) and nonsignificant trends for T_3 and free T_4. There were no gestation-dependent changes in concentrations of maternal hormones.

Maternal concentrations after TRH. Figure 1 shows concentrations of plasma TSH and T_3 in TRH-treated women at delivery. Compared with controls, TSH was elevated approximately 2-fold ($p < 0.05$) in women who received the last dose of TRH 2–4 h before delivery (Fig. 1*a*). For women delivering 5–36 h after the last TRH treatment, TSH concentrations were slightly decreased (66–72% of control, NS after adjusting for multiple comparisons).

Maternal concentrations of T_3 were increased after TRH treatment but reached statistical significance only for those women delivering 13–24 h after the last dose (+57%). In women delivering at later times, levels of T_3 were not different from control (Fig. 1*b*). Plasma concentrations of free T_4 (data not shown) were higher in treated women delivering up to 36 h after the last dose of TRH (range at different time intervals 13.3–14.2 pmol/L *versus* control 11.2 ± 0.5 pmol/L, NS after adjusting for multiple comparisons); values at the two later time intervals were not significantly different from control. Maternal concentrations of PRL were decreased ~40% in women delivering 2–6 h after the last dose of TRH (71.8 ± 15 μg/L, NS after adjusting for multiple comparisons) but were not different from control at later time intervals.

Cord concentrations after TRH. Figure 2 shows the time course for concentrations of thyroid hormones and PRL in cord plasma. Maximal levels of TSH (18.8 ± 2.5 mU/L, $n = 9$) occurred at 2–4 h after the last dose of TRH and were nearly double the control level (Fig. 2*a*). At 5–6 h (not shown), the TSH concentration was similar to control (8.25 ± 1.57 mU/L), and by 13–24 h, the level was significantly decreased (38% of control). TSH values increased progressively at later time intervals and were similar to control at 49–240 h after the last dose.

The concentration of T_3 in cord plasma of 2- to 6-h treated infants (1.2 ± 0.2 nmol/L, $n = 9$) was increased approximately 2-fold *versus* control (Fig. 2*b*). Levels at subsequent intervals decreased progressively, reaching 0.3 nmol/L (46% of control, $p < 0.05$) at 25–36 h. T_3 concentrations increased at later intervals and approached the control value by 49–240 h.

The concentration of free T_4 in cord plasma (Fig. 2*c*) was also increased at 2–6 h after TRH treatment (+19% *versus* control, NS after adjusting for multiple comparisons), and levels were slightly decreased (84% of control) at 49–240 h after treatment.

When data for cord PRL were analyzed for all infants of 26–34 wk gestation, there were no significant differences between control and treated groups (treated 2–6 h 88.3 ± 22.5 μg/L *versus* control 67.6 ± 5.3 μg/L). However, because 12 of the 14 infants delivering 2–6 h after the last treatment were ≤30 wk of gestational age, and because cord PRL increases markedly during gestation, we reanalyzed the data for infants of 26–30 wk (Fig. 2*d*). In these infants, PRL was increased more than 2-fold at 2–6 h after TRH treatment compared with control infants of 26–30 wk; values at subsequent intervals were not different from control.

To examine the response to repeated treatment with TRH, we analyzed data by the number of doses of TRH. Figure 3 shows data for T_3 and free T_4 at 2–6 h from last treatment (maximal stimulation) plotted *versus* the number of TRH doses. Although the number of samples is limited, the mean levels of both hormones are similarly increased after each dose of TRH. However, it is worth noting that three of the six infants delivered 2–6 h after the 4th dose of TRH had T_3 concentrations in the control range. Levels of cord PRL at 2–6 h were also similar

Table 1. *Concentrations of plasma thyroid hormones and prolactin in control population**

Hormone	Maternal	Cord	Newborn	
			2 h	24 h
TSH (mU/L)	4.0 ± 0.2†	9.7 ± 0.7	15.0 ± 1.2†	8.9 ± 1.1
	(62)	(61)	(51)	(51)
T_3 (nmol/L)	2.4 ± 0.1†	0.6 ± 0.04	1.6 ± 0.1†	1.5 ± 0.1†
	(61)	(57)	(59)	(51)
Free T_4 (pmol/L)	11.2 ± 0.6†	14.5 ± 0.5	19.3 ± 0.9†	8.7 ± 0.9†
	(61)	(62)	(53)	(49)
PRL (μg/L)	119.9 ± 11.6†	67.6 ± 5.3	85.7 ± 8.7	78.7 ± 6.9
	(63)	(61)	(50)	(51)

* Values are mean ± SEM for control women and their infants at a gestational age of 26–34 wk who delivered ≤10 d after entry into the trial. Number of samples assayed is shown in parentheses.

† $p < 0.01$ *vs* cord.

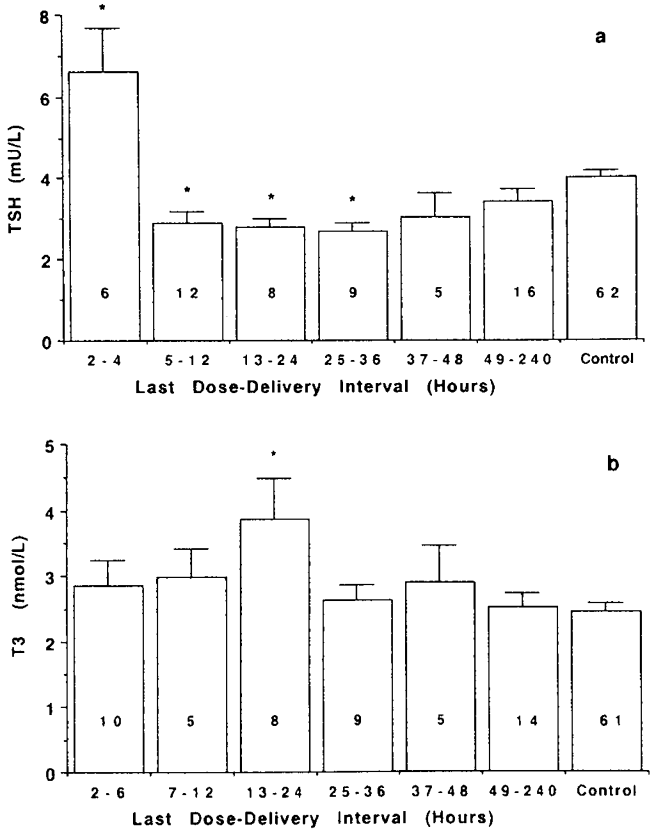

Fig. 1. Concentrations of TSH and T_3 in plasma of women delivering at various intervals after the last dose of TRH. *a*, TSH; *b*, T_3. Values are mean ± SEM, and the number of samples is shown within the *bars*. *, $p < 0.05$ *vs* control. With correction for multiple comparisons, $p > 0.05$ *vs* control for TSH values at 5–36 h.

after each dose of TRH (range of mean values 80–120 μg/L). There were too few values of TSH in the maximally stimulated group (2–4 h) for analysis by number of treatment doses.

We also attempted to analyze the effect of number of treatments on suppression of TSH and T_3. However, because maximal suppression occurred among infants delivered 13–36 h after the last dose of TRH, all of these infants received either three or four (the majority) treatments. Thus, analysis by number of doses was not feasible.

Newborn concentrations after TRH. Blood samples were also obtained from most infants at 2 h of age, at the peak of the normal postnatal T_3 surge, and at approximately 24 h after delivery. Figure 4 shows the values for TSH at 2 h after birth as a function of the time from last TRH dose to delivery. TSH was significantly suppressed in infants delivered 13–48 h after treatment, but the level was similar to control for those delivering 49–240 h after the last dose. At 24 h of age, the concentration of TSH remained low in the group of infants delivered at 2–6 h after treatment (3.3 ± 0.6 mU/L, 37.1% of control) but values for the other treatment groups were not different from control.

Levels of T_3 at 2 h of age were lower than control for treated infants delivering at 2–6 and 25–48 h after the last *in utero* treatment (Fig. 4*b*). The data for infants delivering 7–12 h and 13–24 h after the last dose were more variable, and mean values were not different from control. In samples obtained at 24 h after birth, T_3 remained suppressed in the 2- to 6-h group (0.9 ± 0.2 nmol/L, 60.5% of control) but was normal in the other groups.

Figure 4*c* shows mean values of free T_4 at 2 h of age. Compared with control, levels were slightly but significantly lower for most of the treatment interval groups. In samples obtained at 24 h of age, free T_4 remained less than control for the four treatment groups through 48 h (69–79% of control) but was normal for infants of 49- to 240-h treatment interval.

We further analyzed hormone concentrations after birth by calculating the incremental change from the corresponding value in cord blood. These data are presented in Table 2 for control and treated infants delivering at various intervals after the last *in utero* dose. For TSH, control infants had an average increase of 6.5 mU/L between birth and 2 h of age. By contrast, treated infants delivering at 2–6 h after the last TRH dose had a decrease of approximately 2 mU/L. A similar pattern occurred with T_3, with control infants having a postnatal increase of ~1.1 nmol/L, whereas in treated infants delivered at 2–6 h there was a decrease after birth of ~0.3 nmol/L. Infants delivered at later times after the last dose increased their T_3 concentrations similar to controls. The pattern was similar for free T_4 with an increase in control infants and a decrease or minimal increase for treated infants delivered at 2–48 h.

Postnatal concentrations of PRL were similar in all of the treatment groups (range 50.2–114.3 μg/L) and were not significantly different from the control value. As expected, there was no difference between postnatal and cord values of PRL for either control (Table 1) or treated infants (data not shown).

DISCUSSION

In this study, we assayed concentrations of thyroid hormones and PRL in blood samples obtained from pregnant women and their premature infants who were enrolled in a multicenter trial of antepartum TRH plus glucocorticoid for prevention of newborn lung disease. In this trial, TRH treatment significantly reduced the incidence of chronic lung disease, defined as continuing requirement for supplemental oxygen at 28 d of life (20). The clinical benefit of prenatal TRH is supported by the report of Morales *et al.* (17) and by other preliminary observations (23, 24; D. Knight, G. C. Liggins, unpublished observations). Because this form of therapy may become a generally accepted treatment

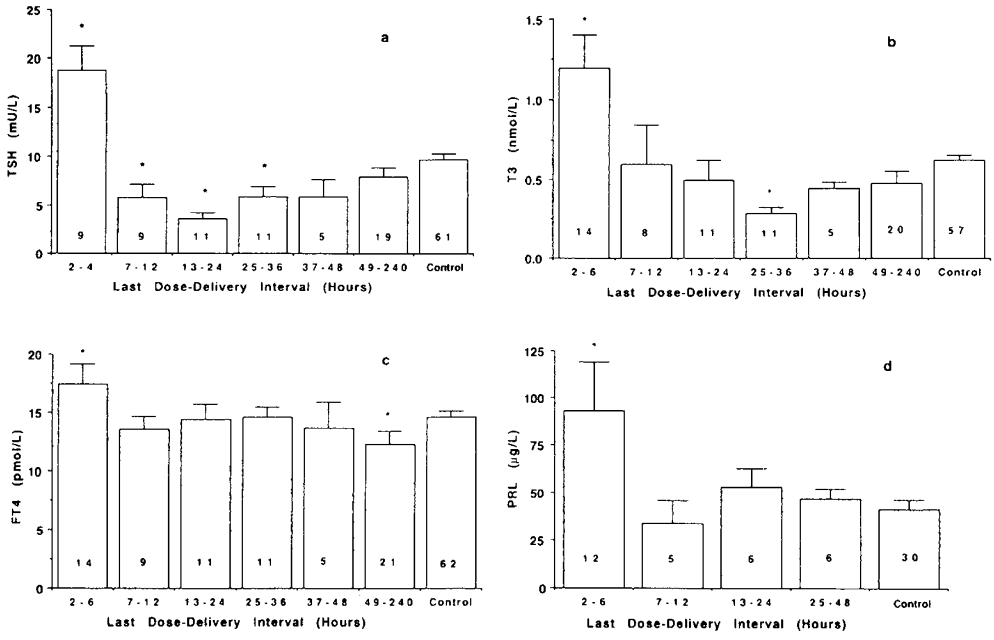

Fig. 2. Concentration of hormones in cord plasma of treated and control infants delivered at various intervals after the last dose of TRH. The gestational age range was 26–34 wk except for analysis of PRL, where the range was 26–30 wk. *a*, TSH; *b*, T_3; *c*, free T_4; *d*, PRL. Values are mean ± SEM, and the number of samples is shown within the *bars*. *, $p < 0.05$ *vs* control. With correction for multiple comparisons, $p > 0.05$ *vs* control for TSH values at 7–12 and 25–36 h and for T_4 values at 2–6 and 49–240 h.

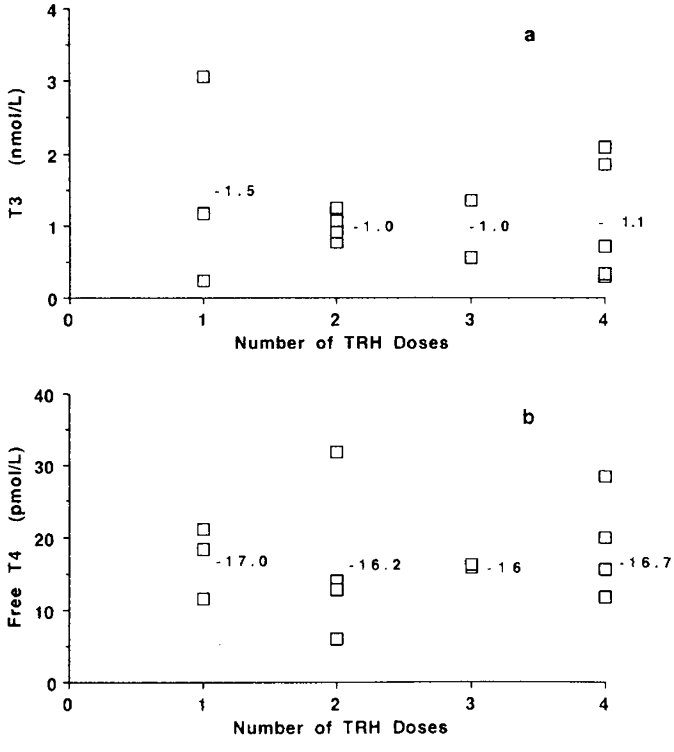

Fig. 3. Cord plasma T_3 and free T_4 for infants delivered 2–6 h after the last dose of TRH: effect of the number of treatments. Individual data and mean values are shown for T_3 (*a*) and free T_4 (*b*) for infants delivered at 2–6 h after one, two, three, or four doses of maternal TRH. Hormone concentrations in the corresponding control population are shown in Table 1: for T_3, $p = <0.001$, 0.006, 0.09, and 0.007 *vs* control at one, two, three, and four doses, respectively; for free T_4, $p = 0.24$, 0.42, 0.55, and 0.01 at one, two, three, and four doses, respectively.

regimen for women in premature labor, we felt it was important to further investigate the effects of TRH on hormone concentrations in the premature infant.

Although we did not have an untreated group in this study, there were no time-dependent changes in thyroid hormone or PRL concentrations in cord blood of the population treated with betamethasone alone (control), and values in cord blood were similar to earlier results for untreated infants (22, 25–29), suggesting that betamethasone did not affect hormone levels. Previously, Osathanondh *et al.* (25) reported increased cord levels of T_3 and reverse T_3 after maternal dexamethasone treatment at term, but no differences were observed with betamethasone therapy before preterm delivery (12). We found no developmental increase in concentrations of TSH in cord plasma at 26–34 wk, in agreement with the findings of Fisher *et al.* (22) but differing from the recent results of Thorpe-Beeston *et al.* (27). The earlier observations of relatively low concentrations of circulating T_3 in the premature fetus plus the observed effects of thyroid hormones on lung maturation in animals and cultured tissue (12) provided the rationale for the clinical study of TRH treatment.

To our knowledge, this study provides the first description of the extended time course of exogenous TRH effects on thyroid hormone concentrations in the premature fetus. We found that the maximal increase of both TSH and T_3 was about 2-fold in cord compared with ~50% in corresponding maternal samples. The maximal fold increase in TSH is less than that previously reported (15–19), likely reflecting the transient nature of the TSH rise and the fact that none of our samples was from infants born less than 2 h after the last dose of TRH. The mean values for T_3 and free T_4 in our study were comparable whether infants delivered after the 1st, 2nd, 3rd, or 4th dose of TRH. The apparent persistence of responsiveness to TRH is in agreement with studies in fetal monkeys in which pretreatment of the fetuses with T_3 did not blunt TRH-stimulated increases in TSH (30).

The increase in fetal T_3 and free T_4 after *in utero* TRH can be considered physiologic in that the maximal levels achieved after treatment are comparable to those normally occurring after birth. Because T_3 concentrations in cord plasma returned to control values by approximately 12 h after treatment, the repeated

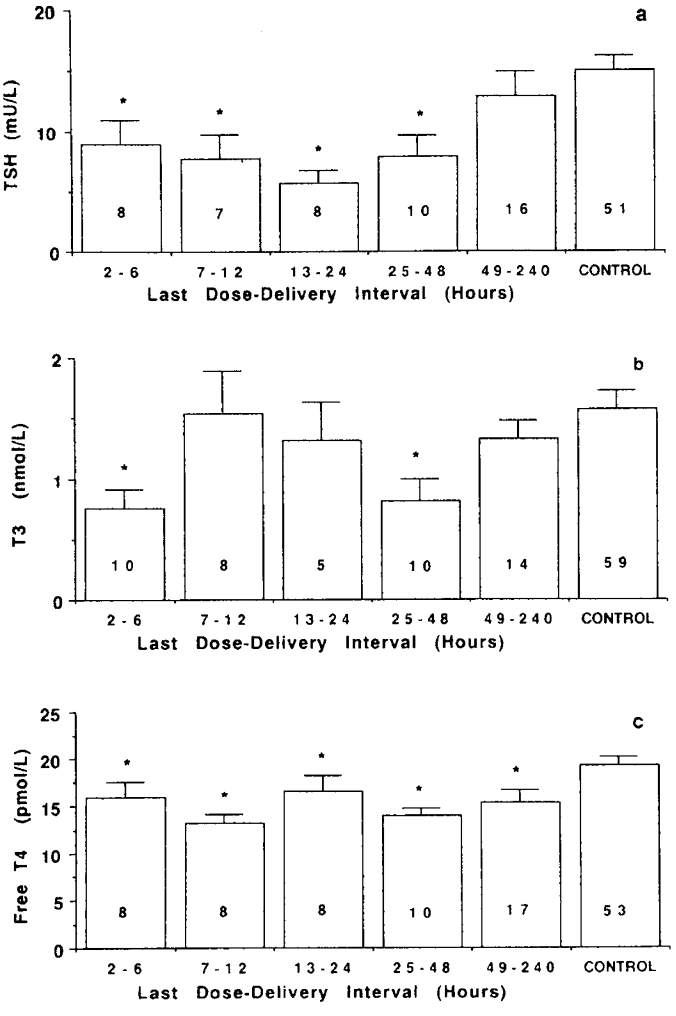

Fig. 4. Plasma hormones at 2 h after birth in infants delivered at various times after the last dose of TRH. *a*, TSH; *b*, T_3; *c*, free T_4. Values are mean ± SEM, and the number of samples is shown within the *bars*. *, $p < 0.05$ *vs* control. With correction for multiple comparisons, $p > 0.05$ *vs* control for TSH values at 2–12 h and for free T_4 values at 2–6 and 13–24 h.

injections of TRH on an 8-h schedule likely do not result in increasingly higher concentrations of plasma T_3 and T_4 with each dose. However, intracellular concentrations of receptor-hormone complex probably remain elevated in target tissues throughout the treatment period of at least 24 h due to the longer $t_{1/2}$ for T_3 in tissue *versus* plasma. Based on responses to T_3 in experimental systems, this exposure time should be sufficient to maximally induce target proteins. Of interest, the clinical benefit of TRH treatment in this study was apparent only in those infants delivering at least 24 h after the first dose (19). The mechanism for reduced chronic lung disease after TRH treatment is uncertain but could involve accelerated development of lung structure, surfactant production, and/or fluid resorption.

Theoretical concerns regarding prenatal TRH treatment are thyrotoxicosis and alterations in learning, behavior, and the pituitary-thyroid axis as have been observed after T_4 treatment of newborn rats. However, the risk of these effects in infants seems low inasmuch as the increase in thyroid hormone concentrations is relatively brief and within the physiologic range. In adults, thyrotoxicosis after TRH is rare and only observed with prolonged treatment (31).

The effect of TRH treatment on concentrations of cord PRL has been controversial. Moya *et al.* (18) found a doubling of cord PRL in infants of 27–34 wk of gestation, whereas Roti *et al.* (19) and Miyamoto (32) found no effect of TRH on PRL 1 h after treatment of women at ~36 wk of gestation and term, respectively. In this study, we found a transient increase in PRL when the comparison was restricted to infants of 26–30 wk of gestation. These various observations suggest that PRL is stimulated by TRH only in the less mature fetuses. It is possible that fetuses closer to term are also responsive, but that the effect is more difficult to observe due to the greater variability of basal levels as gestation proceeds. The failure to observe an increase in maternal PRL as previously reported (29) probably reflects the rapid (maximal at 20 min) and transient increase in their hormone. The possible role of PRL in the beneficial effects of TRH treatment for the premature infant remains uncertain. Although PRL has a permissive role in cortisol effects on lung maturation in the immature fetal lamb (6), a similar effect of PRL in other species, including cultured human lung, has not been established (12).

Previously, Morales *et al.* (17) observed that the mean value for TSH in patients delivering at 1–7 d after TRH treatment was significantly lower than control for both cord and maternal serum, whereas cord levels of T_3 and T_4 were normal. Our data confirm the observation of decreased TSH, indicate that T_3 is also transiently suppressed, and establish the time course for both hormones. Suppression was greater in the fetus than in the mother in whom TSH was only slightly decreased at 5–36 h after treatment and no suppression occurred for T_3 and free T_4. The suppression of TSH after repetitive TRH treatments of pregnant women is in general agreement with earlier observations in adult men and nonpregnant women in whom repetitive TRH treatments decreased basal TSH by approximately 33% (33) and greatly reduced the TSH response to TRH stimulation (31, 33). This suppression has been generally attributed to feedback inhibition of TSH production by the elevated endogenous T_3 and T_4 after TRH stimulation. The reason that the suppression is more marked in the fetus than in the adult is not certain but may be related to the greater increase in fetal *versus* maternal T_3 levels. This mechanism is supported by earlier data that intraamniotic

Table 2. *Incremental changes in thyroid hormone levels after birth**

	Concentration at 2 h of age minus concentration in cord blood					
	0† (control)	2–6†	7–12†	13–24†	25–48†	49–240†
TSH (mU/L)	6.5 ± 1.2 (45)	−1.8 ± 1.1‡ (5)	1.7 ± 1.8 (6)	1.8 ± 1.2 (8)	5.4 ± 3.8 (9)	4.5 ± 1.8 (16)
T_3 (nmol/L)	1.1 ± 0.1 (45)	−0.3 ± 0.3‡ (8)	0.6 ± 0.2 (6)	0.6 ± 0.2 (9)	0.5 ± 0.2 (10)	0.7 ± 0.2 (13)
Free T_4 (pmol/L)	5.0 ± 1.0 (42)	−1.8 ± 1.2‡ (5)	−0.8 ± 1.1‡ (6)	1.2 ± 1.3 (8)	−0.9 ± 1.6 (9)	0.23 ± 0.12 (15)

* Incremental change after birth for the concentration of each hormone was calculated. Mean ± SEM values are shown for infants delivering at various intervals after the last prenatal dose of TRH and for control infants (0 time). The number of samples assayed is shown in parentheses.

† Last dose-delivery interval.

‡ $p < 0.05$ *vs* control.

injection of T_4 decreased basal TSH concentration in cord blood and reduced the postnatal increase in TSH (22).

We also examined the effect of prenatal TRH on the postnatal surge in thyroid hormones. Infants who were born 13–48 h after the last dose of prenatal TRH had significantly decreased postnatal TSH concentrations compared with controls. This finding appears to represent the suppression of TSH (observed *in utero*) plus failure to normally increase TSH after birth (Table 2). In those infants delivered at 2–6 h after treatment, TSH remained below the control level at 24 h of age.

Concentrations of T_3 at 2 h of age were also decreased in recently treated fetuses; however, infants born more than 7 h after the last TRH dose increased their T_3 postnatally in a manner similar to control infants. For recently treated infants (2–6 h), plasma concentrations of both TSH and T_3 decreased from the value at birth rather than increasing. In the study of Moya *et al.* (18), there was a normal postnatal increase in T_3 after one dose of TRH. Our findings suggest that the pituitary-thyroid axis in recently treated newborn infants is either unresponsive to TRH or that the normal increase in endogenous TRH after birth is suppressed. Although the duration of the postnatal suppression in this group of infants remains to be determined, it is most likely transient in view of the time course *in utero*. Postnatal hypothyroxinemia has been described in premature infants and has been ascribed to hypothalamic immaturity. This condition is transient (~6 wk) and appears to be benign with regard to intellectual development (26).

In summary, maternal TRH treatment produces a transient increase in fetal thyroid hormones and PRL to maximal levels approximating those achieved at term or after birth in the premature infant. The kinetics of the increase indicate that TRH treatment should maintain elevated tissue levels of thyroid hormones for at least 24 h. At later times after treatment, fetal thyroid hormones are suppressed, and infants born during the early phase of suppression do not develop the normal postnatal surge of thyroid hormones. The duration of this postnatal suppression remains to be determined.

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