Thyroid hormones (TH) increase metabolism by stimulation of a variety of cell types, and are essential for normal growth and maturation. In many species, fetal serum TH concentrations are low.\(^1\)\(^2\) They increase just before birth and probably play a role in the rapid growth and organ system development that occur in late gestation, as well as in the early postnatal period. In sheep and pigs, gradual increases in fetal cortisol and triiodothyronine (T3) concentrations occur in late gestation, with rapid increases several days before birth.\(^3\)-\(^6\) Prepartum surges of cortisol and T3 also have been demonstrated in foals, although the increases appear to begin later in gestation and continue after birth.\(^7\) Total thyroxine (T4) and T3 concentrations in normal neonatal foals are as much as 14 times higher than those of normal adult horses; free T4 and T3 concentrations are 5 times higher.\(^8\) TH remain very high during the first week of life, and then slowly decrease.\(^8\)-\(^10\) These high concentrations of TH are thought to be important in maintaining thermo-

| Abbreviations: |
|--------------------------------------------------|
| fT3      | free triiodothyronine |
| fT4D     | free thyroxine by equilibrium dialysis |
| NTIS     | nonthyroidal illness syndrome |
| THOP     | transient hypothyroxinemia of prematurity |
| TH       | thyroid hormone(s) |
| TRH      | thyrotropin-releasing hormone |
| TSH      | thyrotropin |
| TT3      | total triiodothyronine |
| TT4      | total thyroxine |

Thyroid function in premature foals has been studied only minimally. Foals born prematurely from early induction of parturition had much lower concentrations of cortisol and total T3 at birth than did full term foals.\(^7\) In a recent larger study, serum TH concentrations were lower in ill premature foals compared to healthy foals, but were not different from those of ill full term foals.\(^15\)

The purpose of this study was to further characterize thyroid function in healthy and sick term and premature foals by measuring serum concentrations of
Materials and Methods

Animals

Three groups of foals were included in this study. The first group consisted of normal full-term foals (gestational age ≥330 days with no clinical signs of prematurity or illness) born to mares belonging to teaching herds at North Carolina State University (NCSU, n = 20, 18 Quarter Horses and 2 Thoroughbreds). During gestation, mares were maintained on Bermuda grass pasture, supplemented as needed with Bermuda grass hay. Between 3 and 4 weeks before their due dates, mares were moved to a small paddock during the day and stalled at night, where they could be more closely monitored before foaling. At that time, they also were introduced to alfalfa and orchard grass hay (14% protein) and 10% protein grain. A physical examination was performed on each normal foal within 36 hours of birth, as well as a complete blood count (CBC), serum biochemistry, arterial blood gas analysis, and serum IgG estimation. Sepsis score was calculated and gestational age recorded. Two additional groups of foals were enrolled into the study by informed consent from the hospital caseloads at the NCSU Veterinary Teaching Hospital in Raleigh, NC (n = 20) and at the Hagyard Equine Medical Institute in Lexington, KY (n = 32). All of the foals from Kentucky were Thoroughbreds. The hospitalized foals from NCSU included 7 Quarter Horse, 4 Tennessee Walking Horse, 3 Thoroughbred, 3 Warmblood, 1 Paint, 1 Appaloosa, and 1 Standardbred foal. Hospitalized foals were designated as either sick foals (gestational age ≥330 days, n = 28) or premature foals (gestational age <330 days with at least 2 clinical signs of prematurity at birth, n = 24). Physical examinations were performed on each hospitalized foal, as well as CBC, serum biochemistry, serum IgG estimation, and blood culture. Sepsis score was calculated and gestational age recorded. Additional tests were performed on these foals as indicated by their illnesses. Hospitalized foals also received treatments and drugs appropriate for their illnesses, as prescribed by their attending clinicians. The study was approved by the NCSU Institutional Animal Care and Use Committee.

Blood Samples

Normal Foals. Blood was obtained by jugular venipuncture from normal term foals at the following ages: <12, 24–36, 48–72 hours, and 5, 7, 10, 14, 21, and 28 days. A TRH stimulation test also was performed in each normal foal at <3 days of age (TRH was injected at <12 h in 2 foals, 24–36 hours in 13 foals, and 42–60 hours in 5 foals). Age at the time of TRH injection was varied slightly because it was anticipated that hospitalized foals would be admitted at various ages. For the TRH stimulation tests, a catheter was placed by using sterile technique into a jugular vein on the morning of the test, several hours before drawing the control blood sample. After the control blood sample was drawn from the catheter, 0.5 mg TRH was given IV, and subsequent blood samples were taken at 15, 30, and 45 minutes, and 1, 2, 4, 6, 8, 12, and 24 hours after TRH administration.

Hospitalized Foals. The study did not interfere with the initial diagnostic evaluation of the foals admitted to either of the 2 hospitals. Once informed consent was obtained, single blood samples were taken to coincide with samples obtained from normal foals at the various ages, and a TRH stimulation test was performed as soon as the foal was stable. TRH stimulation tests could not be performed on all foals, either because of lack of owner consent or physical instability of the foal. Twenty one of 24 premature foals and 20 of 28 sick foals had TRH stimulation tests performed.

Blood samples were allowed to clot at room temperature, centrifuged at 4°C, and serum was removed and stored at −70°C until assayed. All daily samples were assayed for total triiodothyronine (TT3), free triiodothyronine (fT3), total thyroxine (TT4), free thyroxine by equilibrium dialysis (fT4D), and TSH. All samples from the TRH stimulation tests were assayed for TSH; TH were measured in the control and hourly samples.

Hormone Measurement

Serum concentrations of TT3, TT4, fT3, fT4D, and TSH were measured by radioimmunoassay, either with commercially available kits or as previously described and validated in the horse. The TT3 assay sensitivity was 0.3 nmol/L; normal reference range in adult euthyroid horses, 0.7–2.5 nmol/L. The TT4 assay sensitivity was 0.1 pmol/L; normal reference range in adult euthyroid horses, 1.7–5.2 pmol/L. The fT4D assay sensitivity was 3 nmol/L; normal reference range in adult euthyroid horses, 6–46 nmol/L. The fT3 assay sensitivity was 1.8 pmol/L; normal reference range in adult euthyroid horses, 0.02–0.97 ng/mL.

Statistical Analysis

Commercial software was used for statistical analyses and graph generation. Descriptive data for normal TH and TSH concentrations during the first month are presented as mean ± SD. When comparing groups of foals, parametric tests were used for normally distributed data (Shapiro-Wilk); nonparametric tests were used when data were not normally distributed. The t-test or the Mann-Whitney rank sum test was used for 2 groups of foals. Gestational age was compared among normal, sick, and premature foals by ANOVA, with pairwise comparisons performed by the Holm-Sidak method. Sepsis score and TH were used for 24–36 hours were compared among normal, sick, and premature foals by Kruskal-Wallis one-way ANOVA on ranks, with pairwise comparisons performed by Dunn’s method. Spearman correlations on ranks were analyzed across all groups of foals, as well as in hospitalized foals only, to determine whether there was an association between sepsis score and TH or TSH concentration. Results of TRH stimulation tests were analyzed both as raw data and as percentage increase from control. Data were compared among normal, sick, and premature foals by two-way repeated measures ANOVA on ranks, with pairwise comparisons performed by the Holm-Sidak method. Significance for all tests was set at P < .05. Group comparison data are expressed as the median (95% confidence interval; range) unless otherwise noted.

Results

All normal foals had normal physical examinations and routine laboratory test results, and remained healthy during and after the study period. Gestational
Thyroid Hormone Concentrations in Normal Foals

TH and TSH concentrations in normal foals over the first month of life are shown in Figure 1. Total and free T3 concentrations increased after birth and peaked by 2–3 days of age. Peak TT3 and TT4 concentrations were approximately 10 times the normal reference range for adult horses. The TT3 and TT4 concentrations gradually decreased over time, reaching the upper limits of the normal adult reference ranges by approximately 3–4 weeks of age. Peak fT3 and fT4D concentrations in normal foals at birth also were higher than the normal reference ranges for adult horses, but decreased more quickly to the upper limits of the normal adult reference ranges by approximately 10–14 days. The TSH concentrations were within the normal adult reference range at ≤12 hours after birth, and remained stable over the first month.

Thyroid Hormone Concentrations and Outcome in Hospitalized Foals

When sick and premature foals were combined into 1 group of hospitalized foals, TH and TSH concentrations at 24–36 hours were significantly lower in foals with sepsis scores ≥12 compared to foals with sepsis scores <12 (Table 4). When analyzed as separate groups (sick foals or premature foals), differences in TH concentrations were in the same direction, but the differences were not always significant. All TH concentrations also were negatively correlated with sepsis score (Table 5). There was no significant correlation between TSH and sepsis score.

Comparison of Resting Thyroid Hormone Concentrations among Normal, Sick, and Premature Foals 24–36 Hours after Birth

Sick and premature foals had lower resting concentrations of TT3 and fT3 compared to normal foals at 24–36 hours after birth, but the concentrations of sick and premature foals were not different from each other (Fig 2). The TT4 and fT4D concentrations were not different in sick foals compared to normal foals, whereas TT4 and fT4D concentrations were significantly lower in premature foals compared to either normal or sick foals (Fig 2). TSH concentrations were not different among normal, sick, and premature foals (Fig 2).

Table 1. Gestational age, sepsis score, blood culture results, and outcome in normal and hospitalized foals.

|                        | Normal Foals (n = 20) | Sick Foals (n = 20) | Premature Foals (n = 21) |
|------------------------|-----------------------|---------------------|--------------------------|
| Gestational age (days) | 345 (2.8; 333–355)a   | 340 (3.1; 330–358)b | 314 (3.9; 299–326)c       |
| Sepsis score           | 1.0 (0.6; 0–5)a       | 11.5 (1.7; 4–20)b   | 14 (2.2; 7–24)b           |
| # Positive Blood Culture/# No Growth | Not done             | 6/13 (1 not done)   | 4/15 (2 not done)         |
| # Lived/# Died         | 20/0                  | 15/5                | 10/11                    |

Data expressed as median (95% CI; range) or as number (#) of foals. Groups with different letters are significantly different from each other, P < .05.
Comparison of TRH Stimulation Tests among Normal, Sick, and Premature Foals

Administration of 0.5 mg TRH to normal foals in this study resulted in peak increases in TT3 concentration (42%) and fT3 concentration (60%), 2 hours after injection (Fig 3). Repeated measures analysis of the raw data identified significant differences in both TT3 and fT3 concentrations in sick and premature foals compared to normal foals, but sick and premature foals were not different from each other. When the analysis was performed on percentage increase from control, sick foals had a significantly higher percentage increase in TT3 concentration (108%) compared to normal foals, but these results were not different from those of premature foals. For fT3, sick foals had a significantly higher percentage increase in fT3 concentration (141%) compared to both normal and premature foals. In normal foals, TRH administration resulted in peak increases in TT4 concentration (7%) and fT4D concentration (33%), 4 hours after injection (Fig 3). Repeated measures analysis of the raw data identified significant differences in both TT4 and fT4D among all 3 groups of foals. When the analysis was performed on percentage increase from control, there were no significant differences in the percentage increase in response to TRH for either TT4 or fT4D. Thyrotropin-releasing hormone administration to normal foals resulted in a peak increase in TSH concentration of 55% at 15 minutes after injection. Repeated measures analysis of the raw data identified a significant difference between premature and normal foals (Fig 3). When the analysis was performed on percentage increase from control, both premature and sick foals had a significantly higher TSH response to TRH than did normal foals (223% and 102%, respectively). There was no difference in percentage increase in TSH concentration between sick and premature foals.

Discussion

The finding of high circulating TH concentrations in normal newborn foals in this study (compared to nor-
Table 3. TH and TSH concentrations at 24–36 hours in hospitalized foals that lived versus those that died or were euthanized. TH and TSH concentrations at 24–36 hours in normal foals (all lived) are shown for comparison.

| Hormone | Normal Foals | Sick Foals | Premature Foals | All Hospitalized Foals |
|---------|--------------|------------|-----------------|-----------------------|
|         | Lived (n = 20) | Lived (n = 20) | Died (n = 7) | Lived (n = 10) | Died (n = 13) | Lived (n = 30) | Died (n = 20) |
| TT3 (nmol/L) | 8.2 (0.8; 6.0–11.8) | 4.3 (2.0; 1.3–15.9) | 2.6 (2.8; 0.8–7.8) | 3.8 (1.5; 1.9–7.6) | 1.8 (1.3; 0.4–7.4) | 4.1 (1.4; 1.3–15.9) | 2.5 (1.2; 0.4–7.8)* |
| fT3 (pmol/L) | 10.0 (2.0; 5.6–24.2) | 7.1 (2.2; 1.4–17.6) | 5.2 (2.1; 1.6–6.8)* | 6.0 (3.0; 3.3–14.2) | 4.6 (1.5; 0.8–9.0)* | 6.5 (1.7; 1.4–17.6) | 4.9 (1.1; 0.8–9.0)* |
| TT4 (nmol/L) | 260.5 (16.9; 191–318) | 242 (27; 92–319) | 226 (55; 102–283) | 190 (38; 84–238) | 127 (52; 54–299) | 220 (23; 84–319) | 178 (38; 54–299) |
| fT4D (pmol/L) | 97.5 (13.6; 49–144) | 82 (18; 32–176) | 74 (17; 50–98) | 66 (16; 42–116) | 37 (12; 17–94)* | 79 (13; 32–176) | 46 (11; 17–98)* |
| TSH (ng/mL) | 0.24 (0.07; 0.10–0.68) | 0.32 (0.11; 0.06–0.83) | 0.25 (0.10; 0.13–0.48) | 0.30 (0.08; 0.14–0.56) | 0.16 (0.06; 0.09–0.36)* | 0.30 (0.08; 0.06–0.83) | 0.21 (0.05; 0.09–0.48)* |

Results expressed as median (95% CI; range). Asterisk (*) indicates significant difference died versus lived, P < .05, within each foal group (sick, premature, or all hospitalized foals). TT3, total triiodothyronine; fT3, free triiodothyronine; TT4, total thyroxine; fT4D, free thyroxine by equilibrium dialysis; TH, thyroid hormone; TSH, thyrotropin.

Table 4. TH and TSH concentrations at 24–36 hours in hospitalized foals with a sepsis score <12 (low) versus those with a sepsis score ≥12 (high). TH and TSH concentrations at 24–36 hours in normal foals (all sepsis score <12) are shown for comparison.

| Hormone | Normal Foals | Sick Foals | Premature Foals | All Hospitalized Foals |
|---------|--------------|------------|-----------------|-----------------------|
|         | Sepsis Score <12 (n = 20) | Sepsis Score ≥12 (n = 10) | Sepsis Score <12 (n = 9) | Sepsis Score ≥12 (n = 14) | Sepsis Score <12 (n = 22) | Sepsis Score ≥12 (n = 24) |
| TT3 (nmol/L) | 8.2 (0.8; 6.0–11.8) | 2.3 (2.2; 1.2–11.4)* | 3.8 (2.1; 0.9–7.6) | 2.1 (0.9; 0.4–5.5)* | 4.9 (1.7; 0.9–15.9) | 2.3 (1.0; 0.4–11.4)* |
| fT3 (pmol/L) | 10.0 (2.0; 5.6–24.2) | 2.8 (2.4; 1.4–11.4)* | 6.0 (3.4; 2.6–13.4) | 4.8 (2.0; 0.8–14.2) | 6.8 (2.0; 2.2–17.6) | 4.2 (1.4; 0.8–14.2)* |
| TT4 (nmol/L) | 260.5 (16.9; 191–318) | 210 (51; 92–319) | 188 (45; 84–238) | 126 (44; 54–299) | 230 (25; 84–283) | 151 (33; 54–319)* |
| fT4D (pmol/L) | 97.5 (13.6; 49–144) | 70 (18.7; 34–115) | 63 (20.8; 24–103) | 40 (13.8; 17–116)* | 76 (16; 24–176) | 45 (11; 17–116)* |
| TSH (ng/mL) | 0.24 (0.07; 0.10–0.68) | 0.27 (0.16; 0.06–0.75) | 0.26 (0.11; 0.11–0.56) | 0.29 (0.07; 0.11–0.44) | 0.31 (0.10; 0.09–0.83) | 0.29 (0.07; 0.06–0.75) |

Results expressed as median (95% CI; range). Asterisk (*) indicates significant difference sepsis score ≥12 versus sepsis score <12, P < .05, within each foal group (sick, premature, or all hospitalized foals). TT3, total triiodothyronine; fT3, free triiodothyronine; TT4, total thyroxine; fT4D, free thyroxine by equilibrium dialysis; TH, thyroid hormone; TSH, thyrotropin.
mal adults) is in agreement with previous studies in foals.\(^8\)–\(^{10,15,22}\) The increase in T3 concentration over the first few days has been reported previously in foals\(^8\) and humans,\(^11\) and has been suggested to be caused by increased peripheral conversion of T4 to T3.\(^{11}\) To the author’s knowledge, there has been only 1 previous study that measured TSH concentration in foals.\(^{23}\) Results of that study were qualitatively similar.

Table 5. Correlation coefficients and \(P\) values for Spearman rank order correlations between sepsis score and thyroid hormone(s) or thyrotropin concentration at 24–36 hours in sick and premature hospitalized foals or in all 3 groups of foals (normal, sick, and premature).

| Hormone       | Hospitalized Foals Only Sick and Premature (n = 45) | All Foals Normal, Sick, and Premature (n = 65) |
|---------------|--------------------------------------------------|-----------------------------------------------|
|               | \(P\)     | rho      | \(P\)     | rho      |
| TT3 (nmol/L)  | .000263   | −0.522   | .000000200 | −0.718   |
| fT3 (pmol/L)  | .00108    | −0.474   | .0000000326 | −0.629   |
| TT4 (nmol/L)  | .00601    | −0.405   | .0000215    | −0.505   |
| fT4D (pmol/L) | .0000778  | −0.558   | .00000121   | −0.601   |
| TSH (ng/mL)   | .181      | −0.203   | .604        | −0.065   |

TT3, total triiodothyronine; fT3, free triiodothyronine; TT4, total thyroxine; fT4D, free thyroxine by equilibrium dialysis; TSH, thyrotropin.

Fig 2. Resting thyroid hormone (TH) and thyrotropin (TSH) concentrations at 24–36 hours after birth in 20 normal foals, 27 sick foals, and 23 premature foals. Panel A: TT3, B: fT3, C: TT4, D: fT4D, E: TSH. Groups with different letters are significantly different from each other, \(P < .05\). TT3, total triiodothyronine; fT3, free triiodothyronine; TT4, total thyroxine; fT4D, free thyroxine by equilibrium dialysis.
to results of this study, in that resting TSH concentrations in foals were the same as in adult horses. However, TSH concentrations were quantitatively higher for both foals and mares in that study, compared to both the present study and previous studies of TSH in adult horses.\(^{24–29}\) Reasons for the quantitative differences are not clear, although they may have been assay-related.

The observation that TSH concentration is the same in foals as in adult horses was unexpected. TSH concentrations in human newborns have been reported to be 3–10X adult concentrations.\(^{12,30–32}\) In humans, TSH concentration increases rapidly soon after birth, peaks at 12–36 hours, and then slowly decreases over the first few weeks of life. It has been suggested that the initial TSH surge is caused by cold shock, and that the subsequent gradual decrease in TSH concentration is caused by increased TH concentrations and maturation of feedback control.\(^{12,30}\) Possible explanations for higher TH concentrations in foals (compared to adults) without proportionally higher TSH concentrations include increased sensitivity of TSH receptors in the foal thyroid gland, decreased feedback inhibition by TH on the foal hypothalamus and pituitary gland, increased bioactivity of foal TSH compared to adult TSH, or some combination of the these factors. Thus, foals appear to have a different hypothalamic-pituitary-thyroid axis compared to adults.

This study provides further evidence of NTIS in both term and premature foals that are ill. NTIS has been well described in humans, dogs, and cats suffering from systemic diseases, and it has been described preliminarily in adult horses\(^{19,20}\) and foals.\(^{9,10,15}\) TT3 concentration decreases even in mild disease, with or without decreased fT3 concentration, followed by decreased TT4 concentration as disease severity increases.\(^{33–35}\) TSH concentration typically remains inappropriately normal or even low in severe
Higher morbidity and mortality. 12,30,36 NTIS is associated with loss of TRH gene expression, probably from decreased caloric intake (and associated decreases in leptin) and inflammatory cytokines. Sepsis and inflammation increase 5′-deiodinase activity in tanycytes that line the floor or the third ventricle, resulting in increased local T3 production and inhibition of TRH synthesis. Inflammatory cytokines and glucocorticoids also exert negative feedback on TSH release from the pituitary gland, decrease thyroxine-binding globulin concentration and hormone binding capacity, and suppress peripheral 5′-deiodinase, leading to decreased peripheral conversion of T4 to T3.

In the present study, TH concentrations were significantly lower in hospitalized foals with sepsis scores ≥12 compared to those with sepsis scores <12. TH and TSH concentrations also were significantly lower in hospitalized foals that died compared to those that lived, with the exception of TT4. Both sick and premature foals had decreased TT3 and fT3 concentrations compared to healthy foals, without accompanied increases in TSH concentration, consistent with a low T3 state. TT3 and fT3 concentrations were not different between sick term and premature foals. Although TT3 and fT3 concentrations during the TRH stimulation tests were lower in sick and premature foals compared to normal foals, sick and premature foals were able to respond to TRH. All of these T3 observations are consistent with NTIS occurring in both premature and sick foals, with degree of thyroid dysfunction related to severity of illness rather than to maturity. These findings are in good agreement with results of previous studies examining TT3 and fT3 concentrations in healthy foals, without accompanying increases in TSH concentration, consistent with a low T3 state. Premature foals exhibit NTIS, primarily a low T3 state. Premature foals are more markedly hypothyroxinemic than can be accounted for by their severity of illness alone. Given the importance of TH in growth and maturation of many organ systems, low TH concentrations may contribute to morbidity and mortality in sick foals, especially in premature foals.

In summary, normal foals have higher concentrations of TH than do adult horses. Their TH concentrations are the same as those of adults and remain stable, even as TH concentrations decrease into the normal adult range, suggesting an altered hypothalamic-pituitary-thyroid axis which adjusts as foals mature. Sick foals exhibit NTIS, primarily a low T3 state. Premature foals are more markedly hypothyroxinemic than can be accounted for by their severity of illness alone. Given the importance of TH in growth and maturation of many organ systems, low TH concentrations may contribute to morbidity and mortality in sick foals, especially in premature foals.

**Footnotes**

a SNAP Foal IgG Test; IDEXX Laboratories, Inc, Westbrook, ME  
b Angiocath, 16 ga 3 ½”; The Deseret Co, Sandy, UT  
c pGLU-HIS-PRO amide; Sigma Chemical Co, St. Louis, MO  
d Clinical Assays Gammacoat free T4 125I RIA Kit; DiaSorin Inc, Stillwater, MN  
e Clinical Assays Gammacoat M Total T4 125I RIA Kit; DiaSorin Inc  
f Free T4 by equilibrium dialysis; Nichols Institute Diagnostics, San Juan Capistrano, CA  
g Sigmastat/Sigmaplot; Systat Software, Inc, Chicago, IL

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