MEASUREMENTS OF THE EFFECTIVE THYROXINE RATIO (ETR) IN THE NEONATE, INFANT, AND CHILD

L. Shenkman and C. S. Hollander

New York University School of Medicine, New York, New York

The applicability of the effective thyroxine ratio (ETR) was assessed in euthyroid neonates, infants, and children. ETR determinations on cord blood fell within the normal adult range. In contrast, ETR values of newborns age 4 hr to 2 days were all elevated (1.17–1.37) and within the hyperthyroid range for adults. Values in infants age 2 weeks and older and in children age 1–15 years all fell within the normal adult range. These findings suggest that the ETR can be used as an ancillary measure of thyroid function in infants and children. In the immediate postpartum period, however, ETR values may be normally in the adult hyperthyroid range.

Most methods for measuring circulating levels of thyroxine (T_4) can be affected by alterations in concentrations of thyroid-binding proteins. Elevations of thyroid-binding globulin (TBG) levels, therefore, occurring in pregnancy (*1*), in estrogen therapy (*2*), and in acute intermittent porphyria (*3*), will result in higher measurable concentrations of total T_4. These subjects are clinically euthyroid and their circulating free T_4 levels are within the normal range. Similarly, low levels of TBG, as seen in subjects with TBG deficiency or patients receiving androgens, will result in low total T_4 measurements although free T_4 levels are normal.

Several methods have been devised to circumvent this problem. One useful technique is to determine the concentration of T_4 in test serum in the presence of the serum itself and to express it as a fraction of T_4 similarly determined in normal serum [effective thyroxine ratio (ETR)] (*4*). Utilizing this technique, Mincey, et al were able to assess accurately thyroid status of hyperthyroid and hypothyroid patients and euthyroid subjects with and without abnormalities of T_4 binding proteins. Since these studies were done on adult subjects, we assessed the applicability of ETR method in evaluating thyroid status of infants and children.

METHODS

One to two minutes after the delivery of the baby, cord blood was obtained by either manual expression of blood from the severed end of the umbilical cord or by needle aspiration. Blood was collected also from infants age 4 hr–3 months and from children age 1–15 years. All samples were centrifuged immediately after collection and sera were stored at −20°C until analyzed. Using the Mallinckrodt kit, ETR was measured by methods previously described (*4*).

RESULTS

The results of ETR determinations are summarized in Table 1. The mean ETR of cord blood was 1.02, a value which falls well within normal adult levels. In

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For reprints contact: Louis Shenkman, Endocrine Unit, Dept. of Medicine, New York University School of Medicine, 550 First Ave., New York, N.Y. 10016.

TABLE 1. ETR VALUES IN CORD BLOOD AND IN INFANTS AND CHILDREN*

Cord blood	4 hr–2 days	10–12 weeks	1–2 years	2–3 years	3–5 years	5–10 years	10–15 years
1.02 ± 0.02 (9)†	1.23 ± 0.02 (18)†	1.01 ± 0.08 (9)†	0.99 ± 0.06 (8)†	1.01 ± 0.02 (5)†	0.99 ± 0.02 (13)†	1.00 ± 0.03 (14)†	0.98 ± 0.01 (13)†

* Each value represents the mean ± 1 standard even of the mean.
† The number in parentheses indicates the number of subjects studied.

contrast, the ETR values of newborns age 4 hr–2 days were all elevated (1.17–1.37), falling clearly within the hyperthyroid adult range. The ETR levels of infants age 2 weeks–1 month were within the normal adult range. Similarly, ETR values in children age 3 months–1 year were normal as were the values obtained in children age 1–15 years.

DISCUSSION

The period immediately after birth is a dynamic one with regard to thyroid hormone economy. Total T_3 levels in cord blood have ranged from hypothyroid to low normal adult values, and several investigators have observed dramatic rises in serum T_3 and T_4 concentrations within the first days of life (*5–9*). Erenberg, et al have reported that mean T_4 concentrations increased from cord blood levels of 11.9 μg/100 ml to peak values of 16.2 μg/100 ml by 24–48 hr of age while mean serum T_3 levels increased from cord blood levels of 50.5 ng/100 ml to peak values of 419 ng/100 ml (*10*). Free T_3 and T_4 concentrations also rose significantly during the first 2 days of life although mean serum TBG levels were unchanged.

Similar changes in T_3 and T_4 levels during the first 3 days of life were reported by Abuid, et al (*11*).

The current study shows that the transient elevations of circulating thyroid hormones in the first 2 days of life are reflected in the ETR values. While all newborns had normal ETR values in cord blood, samples obtained from newborns, age 4 hr–2 days, all fell within the hyperthyroid range. Samples taken from older children were normal and no age-related alterations were noted up to age 15. It appears, therefore, that the ETR reflects the previously observed transient elevation of thyroid hormones within the first few days of life. Although the T_3 elevations appear more dramatic than the T_4 in the first 2 days of life, it is probably the T_4 elevation that accounts for the rise in ETR. By virtue of its much higher relative concentration, a modest rise in T_4 can serve to occupy many of the available binding sites of thyroid-binding proteins, thereby resulting in the observed elevation of ETR values.

Our findings, therefore, suggest that the ETR can be a useful ancillary measure of thyroid function in newborns and in children. Normal values, comparable to adult levels, can be expected in children. In the immediate postpartum period, however, ETR values may often be in the adult hyperthyroid range.

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REFERENCES

1. DOWLING JT, FREINKEL N, INGBAR SH: Thyroxine binding by sera of pregnant women. *J Clin Endocrinol Metab* 16: 280–281, 1956

2. HOLLANDER CS, GARCIA AM, STURGIS SH, et al: Effect of an ovulatory suppressant on the serum protein-bound iodine and the red-cell uptake of radioactive triiodothyronine. *N Engl J Med* 269: 501–504, 1963

3. HOLLANDER CS, SCOTT RL TSCHUDY DP, et al: Increased protein-bound iodine and thyroxine-binding globulin in acute intermittent porphyria. *N Engl J Med* 277: 995–1000, 1967

4. MINCEY EK, THORSON SC, BROWN JL, et al: A new parameter of thyroid function—the effective thyroxine ratio. *J Nucl Med* 13: 165–169, 1972

5. LARSON PR: Direct immunoassay of triiodothyronine in human serum. *J Clin Invest* 51: 1939–1949, 1972

6. ABUID J, STINSON DA, LARSEN PR: Serum triiodothyronine and thyroxine in the neonate and the acute increases in these hormones following delivery. *J Clin Invest* 52: 1195–1199, 1973

7. FISHER DA, DUSSAULT JH, HOBEL CJ, et al: Serum and thyroid gland triiodothyronine in the human fetus. *J Clin Endocrinol Metab* 36: 397–400, 1973

8. LIEBLICH JM, UTIGER RD: Triiodothyronine in cord serum. *J Pediatr* 82: 290–292, 1973

9. MITSUMA T, AVRUSKIN T, SHENKMAN L, et al: Free and total T_3 and T_4 in pregnant subjects and in neonates. In *Excerpta Medica.* Presented at IV International Congress of Endocrinology, Abstract No. 522, June 1972

10. ERENBERG A, PHELPS DL, LAM R, et al: Total and free thyroid hormone concentrations in the neonatal period. *Pediatrics* 53: 211–216, 1974

11. ABUID J, KLEIN AH, FOLEY TP, et al: Total and free triiodothyronine and thyronine in early infancy. *J Clin Endocrinol Metab* 39: 268, 1974