Serum Triiodothyronine and Thyroxine in the Neonate and the Acute Increases in These Hormones Following Delivery

J. ABUID, D. A. STINSON, and P. R. LARSEN

From the Division of Endocrinology and Metabolism, Department of Medicine and the Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213

ABSTRACT Low triiodothyronine (T_3) and high normal thyroxine (T_4) concentrations are present in cord sera from full term infants. To examine this phenomenon further, radioimmunoassay of T_3 and T_4 was carried out in paired maternal and cord sera as well as capillary sera from neonates at different intervals after delivery. Free T_3 and free T_4 concentrations were also estimated in cord and maternal sera by equilibrium dialysis. In 12 paired specimens, the T_3 concentration in cord sera was significantly lower than the maternal level (51±4 vs. 161±11 ng/100 ml, mean ±SE). Mean free T_3 concentration was also lower in the cord samples (0.15±0.02 vs. 0.31±0.04 ng/100 ml), whereas total and free T_4 concentrations were not significantly different. Umbilical vein and artery samples from 11 neonates did not differ significantly in their T_3 and T_4 concentrations. In seven infants the mean T_3 concentration increased from 51±3 ng/100 ml at delivery to 79±13 at 15 min and 191±16 at 90 min. In four other infants the mean T_3 concentration at 24 and 48 h was not significantly different from the 90 min value of the previous group. Less pronounced changes were observed for T_4 which increased from 12.3±2.0 μg/100 ml (mean ±SE) at delivery to 14.1±1.9 at 90 min and appeared to have reached a plateau at approximately twice the cord value by 24–48 h after delivery.

The maternal-fetal gradient observed for free T_3 is further evidence of the autonomy of the fetal thyroid-pituitary axis. The time course of the abrupt increase in serum T_3 in the neonate suggests that it results from the earlier acute increase in serum TSH which occurs shortly after birth. This suggests that the neonatal thyroid contains significant quantities of T_3. Therefore, unavailability of thyroidal T_3 does not appear to explain the low total and free T_3 concentrations present in the sera of newborns.

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INTRODUCTION

We have recently reported that the concentration of triiodothyronine (T_3)[1] in cord sera from full term infants is in the range observed in hypothyroid adults while thyroxine (T_4) levels are in the high normal adult range (1). The reason for this discrepancy is not immediately apparent. In order to examine this phenomenon more closely and to determine whether free T_3 concentration was also decreased, paired maternal and cord sera as well as capillary samples from neonates were examined. In addition, the relative changes in T_3 and T_4 in the neonate were compared during the period of endogenous thyroid stimulating hormone (TSH) release which normally occurs at the time of delivery (2).

METHODS

Serum samples were obtained from patients at Magee Women's Hospital, Pittsburgh, Pa., after informed consent of the mother. All were normal pregnancies with either vaginal delivery or elective cesarian section. Maternal samples were taken immediately after delivery or just before hysterotomy. Cord samples were usually obtained by direct puncture of the umbilical vein or artery. Capillary blood from infants was obtained by heel puncture, 400 μl of serum being adequate to measure total T_3 and T_4 levels.

T_3 immunoassay. Radioimmunoassay of T_3 was performed as previously described using 50 and/or 25 μl of serum (1). Incubation and antiserum dilution were adjusted to allow displacement of 10–20% of the tracer T_3 by 12.5 pg

[1] *Abbreviations used in this paper:* DFT_3, dialyzable fraction of T_3; DFT_4, dialyzable fraction of T_4; T_3, triiodothyronine; T_4, thyroxine; TSH, thyroid stimulating hormone.

TABLE I

Total and Free Thyroid Hormone Concentrations in Paired Maternal and Cord Sera

	Maternal			Cord			Maternal			Cord		
	T_3	DFT_3	FT_3	T_3	DFT_3	FT_3	T_4	DFT_4	FT_4	T_4	DFT_4	FT_4
	ng/100 ml	*%*	*ng/100 ml*	*ng/100 ml*	*%*	*ng/100 ml*	*μg/100 ml*	*%*	*ng/100ml*	*μg/100 ml*	*%*	*ng/100 ml*
C. N.	135	0.22	0.30	72	0.30	0.22	18.5	0.012	2.22	12.7	0.016	2.03
S. P.	175	0.18	0.32	52	0.25	0.13	13.8	0.012	1.66	16.2	0.015	2.43
A. W.	135	0.21	0.28	32	0.28	0.09	9.3	0.014	1.30	7.5	0.020	1.50
B. J.	115	0.13	0.15	76	0.24	0.18	14.5	0.008	1.16	18.4	0.015	2.76
C. K.*	198	0.16	0.32	42	0.39	0.16	15.6	0.008	1.09	8.2	0.016	1.31
C. L.	108	0.23	0.25	39	0.27	0.10	8.4	0.013	1.09	9.0	0.017	1.49
J. B.*	174	0.23	0.40	29	0.41	0.12	—	—	—	—	—	—
T. L.*	123	0.40	0.49	46	0.35	0.16	9.6	0.013	1.25	11.7	0.012	1.40
Mean	145	0.22	0.31	49	0.31	0.15	12.8	0.011	1.40	12.0	0.016	1.85
±SEM	12	0.03	0.04	6	0.02	0.02	1.4	0.001	0.16	1.6	0.001	0.22
P‡			<0.025						<0.025			
P§			<0.005						NS			

* Delivered by elective cesarian section.

‡ For the difference in dialyzable fraction (*t* test for paired samples).

§ For the difference in free hormone concentration (*t* test for paired samples).

of unlabeled T_3. Results are the mean of at least two sets of duplicate determinations. All measurements (maternal and infant) of a given subject were performed simultaneously to eliminate interassay variability. T_3 levels in normal adult sera are 110±25 ng/100 ml (SD).

T_4 immunoassay. Radioimmunoassay of T_4 was performed by a method similar to that used for T_3. This will be described in greater detail in a subsequent communication.[2] The T_4 values obtained using this method correlate well with those obtained by the competitive binding protein technique (correlation coefficient, 0.97). The normal range for T_4 in euthyroid adults with normal thyroxine-binding globulin levels is 5.1–11.5 μg/100 ml.

Dialyzable fraction of T_3 and T_4. The dialyzable fraction of T_3 and T_4 (DFT_3 and DFT_4) was determined by a modification of the method of Oppenheimer, Squef, Surks, and Haver (3). [^{131}I]T_3 and predialyzed [^{125}I]T_4 were used in order to obtain simultaneous determinations of both free fractions. Tracer enrichment was less than 2 μg T_4/100 ml and less than 1 μg T_3/100 ml. Serum was diluted 1/25 in Krebs-Ringer phosphate buffer (pH 7.4) containing 0.001 M Na azide prior to dialysis. The dialyzable fraction is calculated as counts per milliliter of dialysate per counts per milliliter of dialysand after trichloroacetic acid precipitation. The mean DFT_3 is 0.29±0.02% (SD) and the mean DFT_4 is 0.022±0.002% (SD) in normal sera.

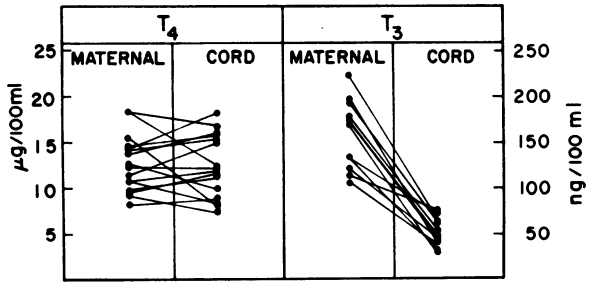

FIGURE 1 Total T_3 and T_4 concentrations in paired maternal and cord sera from full term infants. Samples were obtained from infants after either vaginal delivery (12 pairs for T_4; 8 pairs for T_3) or elective cesarian section (4 pairs for both T_3 and T_4). Cord values correspond to umbilical artery, umbilical vein, or the mean of both determinations.

[2] Submitted for publication.

RESULTS

T_3 and T_4 concentrations in maternal and cord serum. Mean maternal T_3 and T_4 concentrations were 161 ng/100 ml and 12.9 μg/100 ml, slightly above our normal range for both hormones. The mean T_3 value in cord blood was 51 ng/100 ml, significantly lower than the mean for the paired maternal values ($P < 0.001$). The individual pairs are depicted in Fig. 1, and the two- to fivefold difference between the maternal and fetal T_3 values is apparent. The mean T_4 in cord serum was 12.6 μg/100 ml, not significantly different from the maternal level.

In 11 subjects, serum from the umbilical artery and vein were analyzed separately. The mean T_3 concentration in the umbilical artery was 42±3 ng/100 ml (SE) [3] and in the umbilical vein was 43±4 ng/100 ml, not significantly different. There was also no statistical difference in the mean T_4 concentration in these two groups (10.1±0.7 vs. 10.5±0.6 μg/100 ml, respectively).

[3] All subsequent values given will be mean ±SEM unless otherwise indicated.

TABLE II

Serum Thyroid Hormone Levels in Infants During the First 90 Min After Delivery

	T_3			T_4		
	Min after delivery*			Min after delivery*		
Subject	Cord	15	90	Cord	15	90
	ng/100 ml			*μg/100 ml*		
J. B.‡	39	44	166	8.3	9.9	11.1
C. K.‡	42	53	180	8.2	10.0	9.8
P. P.‡	44	78	136	11.6	13.0	14.7
T. L.‡	46	93	204	11.7	—	16.6
R. S.	54	—	230	9.9	—	13.7
S. S.	65	69	231	12.5	12.2	18.9
W. B.	67	136	390§	23.8	23.2	41.6§
Mean	51	79	191	12.3	13.3	14.1
SEM		13	16	2.0	2.5	1.9
P‖		<0.05	<0.001		NS	<0.005

* Times are approximate since 3–5 min were usually required to obtain capillary samples.
‡ Delivered by elective ceasarian section.
§ 120 min sample; not included in calculations.
‖ For difference from cord mean (*t* test for paired samples).

In addition, there was no statistically significant difference between the total cord T_3 and T_4 concentrations in infants following either spontaneous labor or elective cesarian section (for both serum T_3 and T_4, $0.1 > P > 0.05$ by unpaired *t* Test).

Free T_3 and free T_4 concentrations in maternal and cord sera. The mean dialyzable fraction of T_3 was 0.31% in eight specimens of cord serum, significantly greater than the value of 0.22% in maternal samples ($P < 0.025$) (Table I). Nevertheless, the mean free T_3 concentration in the cord sera was 0.15 ng/100 ml, less than one-half of the value in the maternal sera ($P < 0.005$). Despite the slightly higher dialyzable fraction of T_4 in cord sera (0.016% vs. 0.011%), the free T_4 concentrations were not significantly different in the two groups.

Changes in serum T_3 and T_4 concentrations in infants following delivery. As early as 15 min following delivery, slight but statistically significant increases in T_3 concentrations were observed (Table II). The mean T_3 concentration in these infants was 79 ng/100 ml at 15 min as opposed to 52 ng/100 ml at birth. However, a marked increase in the mean total T_3 level to 191 ng/100 ml was observed at 90 min after birth, an almost fourfold increase over the mean cord level. In the case of T_4, the changes observed within this period were less pronounced so that by 15 min no significant increase was detected. By 90 min, the T_4 concentrations were significantly elevated (14.1 vs. 12.3 μg/100 ml at birth).

TABLE III

Changes in Serum T_3 and T_4 During the First 2 Days After Delivery

	T_3			T_4		
Subject	Cord	24 h	48 h	Cord	24 h	48 h
	ng/100 ml			*μg/100 ml*		
C. P.	45	182	141	12.2	25.4	19.3
N. N.*	46	182	127	—	—	—
E. K.	69	353	208	15.2	21.7	23.1
R. S.	54	308	287	9.9	19.9	23.4
Mean	51	262	191	12.4	22.3	21.9
SEM	4	41	37	1.5	1.6	1.3
P‡		<0.025	<0.05		<0.05	<0.05
P§			NS			NS

* Delivered by elective cesarian section.
‡ For difference from cord value (*t* test for paired samples).
§ For difference from 24 h value (*t* test for paired samples).

In the four other infants in whom T_3 concentrations were measured at 24 and 48 h, the levels were significantly elevated over the cord value (Table III). The mean value of 191 ng/100 ml at 48 h did not differ statistically from the value of 262 ng/100 ml at 24 h. In the case of T_4, the 24-h levels were almost twice those at delivery and were essentially unchanged through the next 24 h.

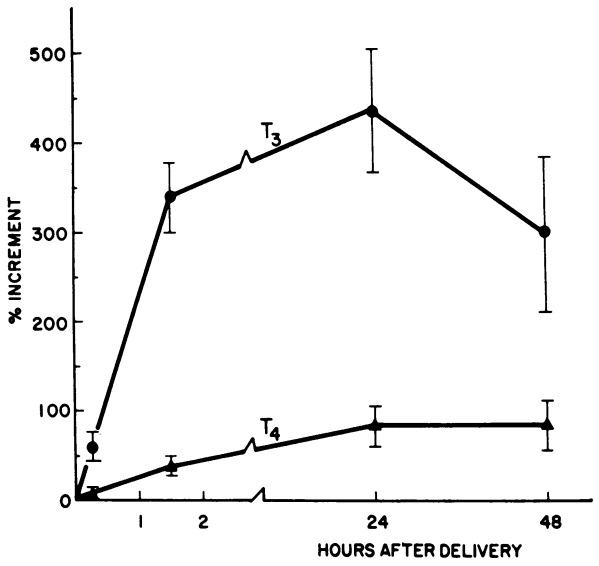

FIGURE 2 Total T_3 and T_4 concentrations in neonatal serum after delivery. Composite representation of the percentage increment in total T_3 and T_4 observed at the different times studied. Values were calculated as the percentage increase relative to the cord value in each subject. The brackets indicate the SEM. The number of samples is listed in Tables II and III.

A composite representation of the relative increments observed at the various times studied shows the differences in the magnitude of the changes for total T_3 and T_4 concentrations (Fig. 2). There is a mean increment of 50% in total T_3 content at 15 min, while at 90 min the T_3 concentration is 300–400% of the cord value. There appears to be no further significant increment at 24 or 48 h. In comparison, the T_4 concentration increased more slowly and appeared to plateau at 24 h at a maximum value which was 190% of the cord level.

DISCUSSION

The low total T_3 and high normal T_4 concentrations found in these cord sera are similar to our previous observations in a smaller group (1). Hotelling and Sherwood, using the Sterling technique for T_3 measurement, have also reported that total T_3 concentration is lower in cord than in maternal sera, though the absolute values reported were higher than those we have obtained (4). The mean T_3 concentration in cord sera is near the mean we have observed in patients with primary hypothyroidism (39±21 ng/100 ml, SD) and appears to be the same in both umbilical artery and vein. The dialyzable fractions of T_3 in maternal and cord sera reported here are in agreement with previous studies by Dussault, Row, Lickrish, and Volpé, though our total T_3 values are much lower due to technical improvements that have occurred since the earlier studies (5, 6). The mean free T_3 concentration in the cord sera, calculated from the total T_3 and dialyzable fraction, is less than one-half of the maternal level as opposed to the free T_4 concentration which is not different. The maternal-fetal gradient for free T_3 indicates there is a placental barrier to the movement of T_3 from mother to fetus. This finding supports previous evidence suggesting that placental transfer of T_3 in the human is incomplete. Earlier reports have shown that in order to cause significant suppression of fetal serum T_4 concentration, quantities of T_3 greatly in excess of physiological requirements (150–300 μg/day) must be administered to the mother (5, 7). Along with the previous demonstration of higher levels of TSH in fetal, as opposed to maternal serum, the maternal-fetal free T_3 gradient is evidence consistent with the hypothesis that the fetal thyroid-pituitary axis functions independently of the mother (8).

The explanation for this phenomenon is not apparent. Current estimates suggest that as much as 40–70% of the circulating T_3 in the adult is derived from peripheral T_4 to T_3 conversion (9, 10). Therefore, the low T_3 level in cord sera could be due to a decreased peripheral T_4 to T_3 conversion in the fetus. Alternatively, it could be due to a lack of T_3 secretion by the fetal thyroid due either to decreased T_3 release or preferential synthesis of T_4 in utero. The latter explanation appears to be unlikely in view of the extremely rapid increase in T_3 concentration observed in the first 90 min of life. This, in turn, probably results from the increased secretion of TSH which occurs at birth with peak levels found at age 30 min (2). If so, it would appear to be indicative of adequate thyroidal T_3 stores. If the rapid increase in T_3 concentration were to be derived from a rapid increase in T_4 to T_3 conversion, the rate of this process would have to be severalfold greater than the rate in adults to account for the abrupt increase in T_3 concentration. Furthermore, T_4 to T_3 conversion would have to decrease just as rapidly to account for the steadily increasing ratio of serum T_4 to serum T_3 after age 1–2 h, when significant increases in the serum T_4 concentrations begin to appear (Fig. 2). The interpretation of these increases in serum T_3 and T_4 concentrations observed after birth as being a result of endogenous TSH secretion is made more attractive by the similarity of the pattern of these changes to the relative increases in serum T_3 and T_4 in adults following exogenous TSH. In the euthyroid adult, the relative increase in serum T_3 concentration is also greater and earlier than the increase in the serum T_4 concentration (1, 10). While this analysis would appear to be valid in general, final determination of the relative changes in the actual secretion rates of T_3 and T_4 cannot be made without knowledge of the metabolic clearance rates of both hormones during this period.

It is possible that the low free T_3 concentration in fetal serum could explain the slight elevation previously observed in fetal serum TSH in the presence of normal free T_4 levels (8, 11). It is also possible that this low free T_3 triggers the TSH release at delivery. However, this interpretation implies an abrupt change in the hypothalamic-pituitary sensitivity to free T_3 levels from the state which exists prior to delivery. Whether or not such a change occurs is an area for current speculation and further study.

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