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Research Article

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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 \pm 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 μ g/100 ml (mean \pm 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 thy-

roid 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.

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 μ l of serum being adequate to measure total T_3 and T_4 levels.

T₃ immunoassay. Radioimmunoassay of T_3 was performed as previously described using 50 and/or 25 μ l 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:* DFT₃, dialyzable fraction of T_3 ; DFT₄, dialyzable fraction of T_4 ; T_3 , triiodothyronine; T_4 , thyroxine; TSH, thyroid stimulating hormone.

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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 T₃. 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. T₃ levels in normal adult sera are 110±25 ng/100 ml (SD).

T₄ immunoassay. Radioimmunoassay of T₄ was performed by a method similar to that used for T₃. This will be described in greater detail in a subsequent communication.² The T₄ values obtained using this method correlate well with those obtained by the competitive binding protein technique (correlation coefficient, 0.97). The normal range for T₄ in euthyroid adults with normal thyroxine-binding globulin levels is 5.1–11.5 μg/100 ml.

Dialyzable fraction of T₃ and T₄. The dialyzable fraction of T₃ and T₄ (DFT₃ and DFT₄) was determined by a modification of the method of Oppenheimer, Squef, Surks, and

Haver (3). [¹²⁵I]T₃ and predialyzed [¹²⁵I]T₄ were used in order to obtain simultaneous determinations of both free fractions. Tracer enrichment was less than 2 μg T₄/100 ml and less than 1 μg T₃/100 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 DFT₃ is 0.29±0.02% (SD) and the mean DFT₄ is 0.022±0.002% (SD) in normal sera.

RESULTS

T₃ and T₄ concentrations in maternal and cord serum. Mean maternal T₃ and T₄ concentrations were 161 ng/100 ml and 12.9 μg/100 ml, slightly above our normal range for both hormones. The mean T₃ 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 T₃ values is apparent. The mean T₄ 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 T₃ 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 T₄ 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.

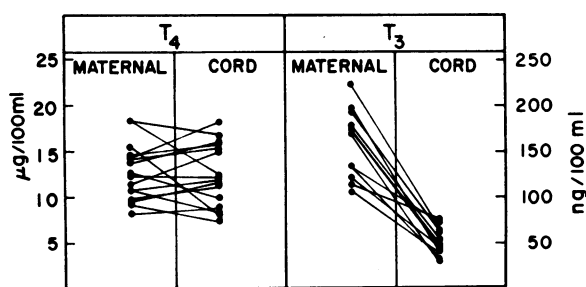


FIGURE 1 Total T₃ and T₄ concentrations in paired maternal and cord sera from full term infants. Samples were obtained from infants after either vaginal delivery (12 pairs for T₄; 8 pairs for T₃) or elective cesarian section (4 pairs for both T₃ and T₄). Cord values correspond to umbilical artery, umbilical vein, or the mean of both determinations.

² Submitted for publication.

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

Subject	T ₃			T ₄		
	Min after delivery*			Min after delivery*		
	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 cesarian 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 T₃ and T₄ concentrations in infants following either spontaneous labor or elective cesarian section (for both serum T₃ and T₄, 0.1 > *P* > 0.05 by unpaired *t* Test).

Free T₃ and free T₄ concentrations in maternal and cord sera. The mean dialyzable fraction of T₃ 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 T₃ 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 T₄ in cord sera (0.016% vs. 0.011%), the free T₄ concentrations were not significantly different in the two groups.

Changes in serum T₃ and T₄ concentrations in infants following delivery. As early as 15 min following delivery, slight but statistically significant increases in T₃ concentrations were observed (Table II). The mean T₃ 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 T₃ 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 T₄, the changes observed within this period were less pronounced so that by 15 min no significant increase was detected. By 90 min, the T₄ concentrations were significantly elevated (14.1 vs. 12.3 μg/100 ml at birth).

TABLE III
Changes in Serum T₃ and T₄ During the First 2 Days After Delivery

Subject	T ₃			T ₄		
	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 T₃ 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 T₄, the 24-h levels were almost twice those at delivery and were essentially unchanged through the next 24 h.

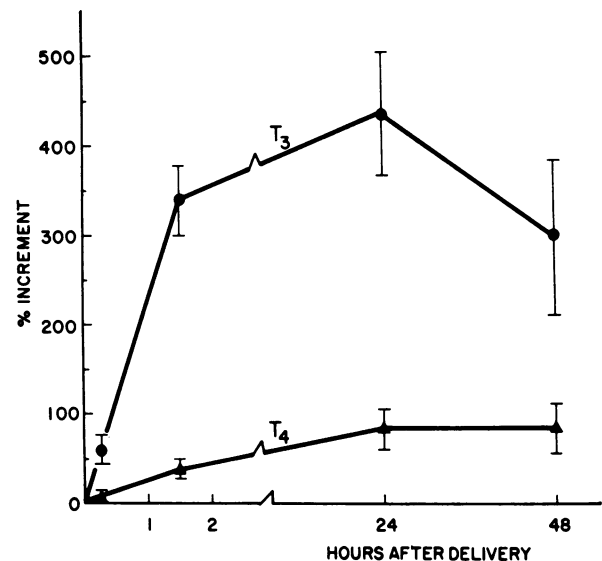


FIGURE 2 Total T₃ and T₄ concentrations in neonatal serum after delivery. Composite representation of the percentage increment in total T₃ and T₄ observed at the different times studied. Values were calculated as the percentage increase relative to the cord value in each subject. The brackets indicate 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 T₃ and T₄ concentrations (Fig. 2). There is a mean increment of 50% in total T₃ content at 15 min, while at 90 min the T₃ concentration is 300–400% of the cord value. There appears to be no further significant increment at 24 or 48 h. In comparison, the T₄ 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 T₃ and high normal T₄ 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 T₃ measurement, have also reported that total T₃ concentration is lower in cord than in maternal sera, though the absolute values reported were higher than those we have obtained (4). The mean T₃ 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 T₃ in maternal and cord sera reported here are in agreement with previous studies by Dussault, Row, Lickrish, and Volpé, though our total T₃ values are much lower due to technical improvements that have occurred since the earlier studies (5, 6). The mean free T₃ concentration in the cord sera, calculated from the total T₃ and dialyzable fraction, is less than one-half of the maternal level as opposed to the free T₄ concentration which is not different. The maternal-fetal gradient for free T₃ indicates there is a placental barrier to the movement of T₃ from mother to fetus. This finding supports previous evidence suggesting that placental transfer of T₃ in the human is incomplete. Earlier reports have shown that in order to cause significant suppression of fetal serum T₄ concentration, quantities of T₃ 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 T₃ 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 T₃ in the adult is derived from peripheral T₄ to T₃ conversion (9, 10). Therefore, the low T₃ level in cord sera could be due to a decreased peripheral T₄ to T₃ conversion in the fetus. Alternatively, it could be due to a lack of T₃ secretion by the fetal thyroid due either to decreased T₃ release or preferential synthesis of T₄ in utero. The latter explanation appears to be un-

likely in view of the extremely rapid increase in T₃ 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 thyroïdal T₃ stores. If the rapid increase in T₃ concentration were to be derived from a rapid increase in T₄ to T₃ conversion, the rate of this process would have to be severalfold greater than the rate in adults to account for the abrupt increase in T₃ concentration. Furthermore, T₄ to T₃ conversion would have to decrease just as rapidly to account for the steadily increasing ratio of serum T₄ to serum T₃ after age 1–2 h, when significant increases in the serum T₄ concentrations begin to appear (Fig. 2). The interpretation of these increases in serum T₃ and T₄ 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 T₃ and T₄ in adults following exogenous TSH. In the euthyroid adult, the relative increase in serum T₃ concentration is also greater and earlier than the increase in the serum T₄ 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 T₃ and T₄ cannot be made without knowledge of the metabolic clearance rates of both hormones during this period.

It is possible that the low free T₃ concentration in fetal serum could explain the slight elevation previously observed in fetal serum TSH in the presence of normal free T₄ levels (8, 11). It is also possible that this low free T₃ triggers the TSH release at delivery. However, this interpretation implies an abrupt change in the hypothalamic-pituitary sensitivity to free T₃ 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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