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Fetus thyroxine
newborn triiodothyronine
placenta

Serum Triiodothyronine, Total Thyroxine, and Thyroxine to Triiodothyronine Ratios in Paired Maternal-Cord Sera and at One Week and One Month of Age

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Extract

Twenty-seven paired maternal-cord sera were analyzed for serum triiodothyronine (T_3), total serum thyroxine (TT_4), and maximum thyroxine globulin binding capacity (TBG cap.). In 17 of the infants the same studies were repeated at 1 week of age and in 10 of the 17 at 1 month. The mean T_3 value for the cord sera was 73.1 ± 20.4 ng/100 ml while the mean value for the maternal sera was 204 ± 49.2. The difference in the mean values was highly significant ($P < 0.001$). The maternal T_3 values are comparable with those of nonpregnant control subjects; those of cord blood fall below normal values. No statistically significant difference was found between the TT_4 and TBG cap. values for cord and maternal sera. Both values were higher than the normal nonpregnant control values. At 1 week of age the serum T_3 levels had increased to a mean of 208.4 ± 40.9 ng/100 ml. This mean is significantly different from the one observed in cord sera ($P < 0.001$). A significant increase in the TT_4 values, mean 12.53 ± 2.2 μg/100 ml ($P < 0.01$), was observed by the end of the 1st week. TBG cap. did not change significantly between birth and 1 week of age; by the end of the 1st month of life the serum TT_4 had decreased significantly to a mean of 9.5 ± 2.7 μg/100 ml ($P < 0.05$), while the serum T_3 was maintained at a mean level of 228.2 ± 16.9 ng/100 ml, a value not significantly different from the one observed at 1 week of age.

Speculation

The extremely low levels of T_3 in the cord blood in the presence of TT_4 and TBG cap. values equal to those of the maternal blood suggest minimal materno-fetal placental transfer of T_3. We have postulated that the low fetal T_3 is responsible for the high levels of pituitary thyrotropic hormone (TSH) present in cord blood and early in the postnatal period and that the high levels of TT_4 with normal T_3 levels observed by the end of the 1st week of life indicate defective peripheral deiodination of thyroxine (T_4) to T_3 and account for the lack of signs and symptoms of hyperthyroidism. By the end of 1 month of age TT_4 and T_3 values are within normal ranges, which indicates maturation in the metabolic pathway of T_4 and T_3.

Introduction

Thyroxine metabolism in the neonate is still not completely understood. During the first few days of postnatal life serum hormonal iodine values have been shown to increase significantly [4, 9, 10, 13, 14, 16]. Absence of clinical signs of hyperthyroidism in the presence of laboratory findings suggestive of thyroid hyperactivity continues to be unexplained. Recent evidence that deiodination of (T_4) to (T_3) is a prominent pathway of T_4 metabolism in normal adults and the development of a sensitive radioimmunoassay for measuring stable T_3 in serum [11] prompted the investigation of this pathway of thyroxine metabolism in the newborn period.

Materials and Methods

Twenty-seven paired maternal and cord sera samples were obtained from normal pregnant women who delivered normal full term infants via the vaginal route without complications. Informed consents were obtained from all subjects in accord with the Helsinki Declaration. Seventeen of the infants were followed for the 1st week of life and 10 of the 17 were followed for the 1st month. All samples were analyzed for TT_4, T_3, and TBG cap. The TT_4 was determined by the method of Murphy and Pattee [1, 15], serum T_3 was measured by a radioimmunoassay developed by Gharib *et al.* [11] who used a highly specific antibody. The TBG cap. was estimated using the reverse flow electrophoresis in tris-maleate buffer at pH 8.6 [12, 19]. Thyroxine to triiodothyronine (T_4/T_3) ratios were calculated from the values obtained for each sample.

Results

The results in the twenty-seven paired cord and maternal samples are indicated in Table I. Maternal samples had significantly higher T_3 levels compared with cord blood ($P < 0.001$). The TBG cap. was found to be significantly higher in the mothers' sera than in cord sera ($P < 0.05$). The T_3 values for the maternal sera are comparable with those of nonpregnant control subjects; however, values for cord blood are well below the accepted normal adult values for our laboratory. The thyroxine to triiodothyronine ratios calculated from these values gave a mean T_4/T_3 ratio for the cord blood of 135.2 ± 39.2 whereas that for the maternal sera was 55.1 ± 12. The difference in the ratio is highly significant ($P < 0.001$). The serum levels of triiodothyronine at 1 week of age increased to a mean of 208.4 ± 40.9 ng/100 ml. compared with 73.1 ± 20.4 for the cord blood. Table II is a longitudinal analysis of the T_3 values observed for cord blood at 1 week and at 1 month of age, and those for maternal blood. The Δ *t* test was applied to the data [5]: $\Delta 1$ denotes the change in T_3 values from cord blood to 1 week of age, $\Delta 2$ the change from 1 week to 1 month, and $\Delta 3$ the overall change from cord to 1 month in the individual infant. The test data and the *P* values are recorded at the bottom of the table. As can be seen, a significant increase in T_3 levels occurred from birth to 1 week of age but we did not find a significant change in the T_3 levels between 1 week and 1 month of age. Table III is the longitudinal analysis of the TT_4 values in cord blood, at 1 week and at 1 month of age, and those of the maternal blood. The same statistical analysis used in Table II was used for this data. A significant increase in TT_4 values was found to occur between 1 week and 1 month of age. No significant difference was found in the cord values and those at 1 month of age.

Tables IV and V represent the longitudinal data for TBG cap. and the calculated T_4/T_3 ratios, respectively. As can be seen, there were no significant changes in the TBG cap. between birth and 1 week of age; however, a significant drop took place between 1 week and 1 month. The calculated T_4/T_3 ratios showed a significant drop between 1 week and 1 month. Overall we found a significant drop in T_4/T_3 from cord to 1 month.

Discussion

Our findings of elevated TT_4 and TBG cap. in maternal blood are in accordance with the reports of other investigators who have found these changes to be characteristic of pregnancy [16, 20, 22]. The increase in TBG cap. is secondary to estrogen effects and responsible for the elevation in the TT_4. However, the normal serum T_3 levels observed in the maternal sera indicate that, in contrast to thyroxine, the serum T_3 concentration is not influenced by elevations in TBG cap. These levels are in accordance with the reports that TBG cap. elevation after estrogen therapy does not increase the serum T_3 levels [6]. Cord blood had a significantly lower T_3 concentration than the paired maternal blood. These lower values were observed in the presence of similar concentrations of serum T_4 and TBG

Table I. Triiodothyronine (T_3), total thyroxine (TT_4), thyroxine binding globulin (TBG) concentration, and thyroxine to triiodothyronine ratios (T_4/T_3) in maternal and cord sera

Samples	T_3, ng/100 ml		TT_4, μg/100 ml		TBG, μg/100 ml		T_4/T_3	
	Maternal	Cord	Maternal	Cord	Maternal	Cord	Maternal	Cord
1	248	92.5	10.6	7.3	26.5	26.5	42.7	78.9
2	193	103	>15.3				77.7	
3	174	87	10.7	11.2	30.2		61.5	117.89
4	239	94	6.2		33.0		26.5	
5	229	68		6.7		24.9		95.06
6	167	90	7.0	10.6	20.0	26.5	44.0	132.5
7	151	70						
8	245	86		6.7	41.0	25.1		98.12
9	232	74		9.0				
10	163	63	10.5	6.5	37.5		64.4	114.03
11	183	52	9.6		31.5		52.45	
12	245	76	10.7	11.2	38.6		43.63	147.36
13	115	72	7.3	11.2	21.3		63.47	155.55
14	120	92	6.5	12.5	20.5	32.2	54.16	135.87
15	273	54	10.1	6.6	42.1		35.43	122.0
16	298	61		11.9				195.08
17	288	64	11.8	8.5	38.1		42.75	114.86
18	268	84	6.6		28.4		42.03	
19	165	85	12.4	6.9	34.9	23.9	75.15	88.46
20	157	71	11.6		34.2		56.58	
21	180	103	12.7	11.0	36.6	28.0	70.5	119.56
22	198	83	9.9		35.4		50.0	
23	235	57	13.7	10.4	35.1	27.1	68.29	182.5
24	183	58	12.1	10.3	36.7	28.7	66.12	177.58
25	244	53	11.9	8.8	33.9	22.2	48.7	166.0
26	150	59	10.6	13.5	35.1	25.9	70.6	228.81
27	196	117	10.9	11.5	33.7	22.2	55.6	98.29
Number	27	27	22	20	22	12	22	19
Mean ± SD	204 ± 49.2	73.1 ± 20.4	10.3 ± 2.4	9.6 ± 2.1	32.9 ± 6.0	26.1 ± 2.7	55.1 ± 13.0	135.2 ± 39.2
t Test	13.7		1.8		3.7		9.8	
P	<0.001		<0.1		<0.001		<0.001	

Table II. A comparison of serum triiodothyronine of (T_3) levels with statistical analysis[1]

Sample	T_3, ng/100 ml				Δ1	Δ2	Δ3
	Maternal	Cord	1 Wk	1 Mo			
1	248	92.5	195	167	−102.5	28	−74.5
2	193	103	207		−104		
3	174	87	171	112	−84	59	−25
4	239	94	260		−166		
5	229	68	240	245	−172	−5	−177
6	167	90	288	188	−198	100	−98
8	245	86	214		−128		
10	163	63		239			−176
12	245	76	167	249	−91	−82	−173
13	115	72	154		−82		
14	120	92	224	238	−132	−14	−146
15	273	54	172		−118		
16	298	61		281			−220
17	288	64	153		−89		
18	268	84	273		−189		
23	235	57	224		−167		
24	183	58	217	294	−159	−77	−236
27	196	117	228		−111		
n					16	7	9
$\bar{\Delta}$					−130.78	1.28	−147.27
SE$\bar{\Delta}$					9.77	25.41	23.03
P value					<0.001	NS	<0.001

[1] Δ_1 denotes the change from cord blood to 1 week of age, Δ_2 the change from 1 week to 1 month, and Δ_3 the overall change from cord to 1 month in the individual infant. NS: Not significant.

Table III. A comparison of total thyroxine (TT_4) levels with statistical analysis[1]

Sample	TT_4, μg/100 ml				Δ1	Δ2	Δ3
	Maternal	Cord	1 Wk	1 Mo			
1	10.6	7.3	9.4	7.8	−2.1	1.6	−0.5
3	10.7	11.2	8.9	5.0	2.3	3.9	6.2
5		6.7	9.6	6.0	−2.9	3.6	0.7
6	7.0	10.6	11.2	8.7	−0.6	2.5	1.9
8		6.7	15.3		−8.6		
10	10.5	6.5		7.8			−1.3
12	10.7	11.2	14.3	10.7	−3.1	3.6	0.5
14	6.5	12.5	15.3	12.1	−2.8	3.2	0.4
15	10.1	6.6	12.1		−5.5		
16		11.9		11.9			0
17	11.8	8.5	13.3		−4.8		
23	13.7	10.4	14.3		−3.9		
24	12.1	10.3	12.9	14.1	−2.6	−1.2	−3.8
27	10.9	11.5	15.3		−3.8		
n					12	7	9
$\bar{\Delta}$					−3.20	2.45	0.45
SE$\bar{\Delta}$					0.76	0.67	0.89
P value					<0.01	<0.05	NS

[1] Δ_1 denotes the change from cord blood to 1 week of age, Δ_2 the change from 1 week to one month, and Δ_3 the overall change from cord to 1 month in the individual infant. NS: Not significant.

Table IV. A comparison of maximum thyroxine globulin-binding capacity (TBG) with statistical analysis[1]

Sample	TBG, μg/100 ml				Δ1	Δ2	Δ3
	Maternal	Cord	1 Wk	1 Mo			
1	26.5	26.5	31.5	21.0	−5.0	10.5	5.5
5		24.9		17.7			7.2
6	20.0	26.5	28.7	24.0	−2.2	4.7	2.5
8	41.0	25.1	22.2		2.9		
14	20.5	32.2	31.1	24.0	1.1	7.1	8.2
23	35.1	27.1	24.2		2.9		
24	36.7	28.7	23.2	19.6	5.5	3.6	9.1
27	33.7	22.2	27.6		−5.4		
n					7	4	5
$\bar{\Delta}$					−0.02	6.47	6.50
SE$\bar{\Delta}$					1.59	1.52	1.16
P value					NS	<0.05	<0.011

[1] Δ_1 denotes the change from cord blood to 1 week of age, Δ_2 the change from 1 week to 1 month, and Δ_3 the overall change from cord to 1 month in the individual infant. NS: Not significant.

cap. in maternal and cord sera and indicate little or no transplacental transfer of T_3. These findings are in accordance with recent animal experimentation which has demonstrated that in thyroidectomized fetal lambs, transfer of T_3 across the placenta is minimal [7], but are at a contrast to findings of Dussault *et al.* [6], who found levels of T_3 in cord blood to be similar to those of the maternal blood. The difference in the results may be explained by the different methodology used in the two studies. The low levels of T_3 in the presence of normal T_4 levels in cord blood tend to indicate that in the fetus either T_3 secretion by the fetal gland is decreased or that peripheral conversion of T_4/T_3 is markedly decreased. Pituitary thyrotropic hormone has been shown to be elevated in cord blood and to remain elevated for at least 72 hr after birth [3, 8, 21, 23]. The stimulus for the increased secretion of TSH has not been elucidated. Exposure to cold has been postulated; however, Fisher and Odell [8] demonstrated levels of TSH of the same magnitude as those found in cord blood to be present in blood obtained from scalp veins before delivery. The low circulating

Table V. A comparison of thyroxine to triiodothyronine (T_4/T_3) ratios with statistical analysis[1]

Sample	T_4/T_3 ratios				Δ1	Δ2	Δ3
	Maternal	Cord	1 Wk	1 Mo			
1	42.7	78.9	48.2	46.7	30.7	1.5	32.2
3	61.5	117.9	52.0	44.6	65.9	7.4	73.3
5		95.1	40.0	24.5	55.1	15.5	70.6
6	44.0	132.5	38.9	46.3	93.6	−7.4	86.2
8		98.1	71.5		26.6		
10	64.1	114.0		32.6			81.4
12	43.6	147.4	85.6	43.0	61.8	42.6	104.4
14	54.2	135.9	68.3	50.8	67.6	17.5	85.1
15	35.4	122.0	70.3		51.7		
16		195.1		42.3			152.8
17	42.8	114.9	86.9		28.0		
23	68.3	182.5	63.8		118.7		
24	66.1	177.6	59.4	48.0	118.2	11.4	129.6
27	55.6	98.3	67.1		31.2		
n					12	7	9
$\bar{\Delta}$					62.42	12.64	90.62
$SE\bar{\Delta}$					9.49	5.94	11.68
P value					<0.001	NS	<0.001

[1] Δ_1 denotes the change from cord blood to 1 week of age, Δ_2 the change from 1 week to 1 month, and Δ_3 the overall change from cord to 1 month in the individual infant.

levels of T_3 found in the fetus probably represents the stimulus for TSH hypersecretion *in utero* and for its persistance in the immediate postnatal period. The present data is in agreement with this hypothesis.

Danowski *et al.* [4] were first to report the levels of serum protein-bound iodine (PBI) within the newborn period. Their results indicate that within 12 hr after birth the serum PBI in infants was similar to the one present in the maternal blood at the time of delivery with a gradual increase in the levels reaching a peak by the 3rd day and persisting during the entire 1st week of life. The values observed were higher than their accepted standard values for adult euthyroid subjects. Man *et al.* [13] and Pickering *et al.* [16], who measured thyroxine-like butanol-extractable iodine (BEI), demonstrated that the levels of BEI are similar in maternal and cord sera, but that a sharp increase occurs during the 1st week of life which reaches a peak by the 5th day with a return to values similar to those found in cord blood by the 18–20th day of life. Our findings of similar TT_4 levels in cord and maternal sera with a rise in the circulating levels of TT_4 by 1 week of age and a return to levels equal to those found in the cord blood by 1 month of age are in accordance with the previous data for PBI and BEI in the neonatal period. The marked elevation in TT_4 that takes place in the 1st week of life cannot be explained on the basis of changes in TBG cap., inasmuch as TBG cap. values were found not to change significantly during the 1st week of life (Table IV) the decrease in TBG cap. observed to take place between 1 week and 1 month of age could partially, but not completely, explain the TT_4 changes observed between 1 week and 1 month of age (Table III). We believe a probable explanation for this change to be forthcoming from our data. To our knowledge, serial determinations of serum T_3 levels in the cord blood, at 1 week, and at 1 month of age have not been previously reported.

Braverman *et al.* [21] were first to demonstrate extrathyroidal conversion of T_4 to T_3 in man. Pittman *et al.* [18], in a study of the kinetics of T_4 to T_3 conversion in normal adults, demonstrated that the average daily rate of the extrathyroidal conversion of T_4 to T_3 was 33% of the total thyroxine production and that the amount of T_3 generated by this pathway contributed 41% of daily total T_3 production. This data proves that extrathyroidal conversion of T_4 to T_3 is a major metabolic pathway of T_4 in normal adults. An equally important, but less efficient, metabolic pathway of T_4 in the newborn period can be postulated from our data, which shows that the rapid increase in the circulating levels of T_3 observed by the end of the 1st week of life is associated with abnormally high levels of circulating T_4 without significant changes in TBG

cap. A defective peripheral conversion of T_4 to T_3 would account for these findings, as well as for the absence of clinical signs of hyperthyroidism in the presence of high circulating levels of T_4 and TSH. Without kinetic data we cannot exclude defective thyroidal production of T_3; however, the ability of the neonatal thyroid to raise the circulating levels of T_4 to abnormally high levels makes defective peripheral conversion of T_4 to T_3 a more attractive hypothesis; the decrease in circulating levels of T_4 to normal values with maintenance of normal circulating levels of T_3 observed by 1 month of age tends to indicate a progressive maturation in the metabolic pathways of T_4 and T_3. This progressive maturation of enzyme systems is characteristic of the newborn period.

Summary

Our data shows that in the fetus, the T_3 levels are extremely low, whereas levels of TT_4 and TBG cap. are comparable with those of the mother. Maternal T_3 was not elevated compared with values for nonpregnant subjects, which indicates that TBG cap. elevation does not have a significant effect on circulating T_3 levels. The low fetal T_3 levels suggest little placental transfer. The circulating levels of T_3 had a significant increase by the end of the 1st week of life; this increase was associated with abnormally high levels of circulating TT_4 without significant changes in TBG cap. A decrease in TT_4 to levels equal to those found in cord blood but with maintenance of normal circulating T_3 levels was achieved by 1 month of age.

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