Shimane J. Med. Sci. Vol. 2, pp. 167–175, 1978

Studies on the Pituitary Body-Thyroid Gland System of Fetus and Response to Labor as Viewed from TSH, T_4, T_3, rT_3 and Thyopac-3

(maternal blood/umbilical arterial blood)

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(Received December 16, 1978)

The TSH, T_4, T_3, rT_3 and Thyopac-3 levels in maternal blood and umbilical arterial blood were determined for a better management of labor, delivery and of the newborn immediately after delivery.

The TSH level in both maternal and umbilical arterial blood immediately after delivery was high, while the T_3 level in umbilical arterial blood was low. Thus it was surmised that the feed-back mechanism of the pituitary body-thyroid gland system of the fetus had been completed.

From the results of T_4, Thyopac-3 and FT_4I, it was deduced that TBG would increase in excess of maternal blood T_4 and that fetal blood T_4 would be secreted to about the same extent in women with a normal thyroid function.

The T_3 level and the T_3/T_4 ratio in maternal blood were high, while the T_3 level and T_3/T_4 ratio in umbilical arterial blood were extremely low. Conversely, the rT_3 level and the rT_3/T_4 ratio in maternal blood was low, while the rT_3 level and the rT_3/T_4 ratio in umbilical arterial blood were high.

Thus, there appears to be a reciprocal relationship between T_3 and rT_3 and that these are probably converted from T_4 to T_3 with strong biological activity in the mother and from T_4 to biologically inactive rT_3 in the fetus.

A great variety of hormones are produced in the mother, fetus and placenta. This endocrinological environment is considered to be concerned with fetal adaptation to the mother, the mother-fetus defense mechanism against labor stress and the mechanism by which the fetus adapts itself to the extrauterine environment.

Elucidating the endocrinological dynamics, particularly at labor when not only the mother but also the fetus is subject to stress, appears to be of significance for the management of labor and of the newborn.

Although there are reports on the dynamics of the pituitary body-adrenal gland system under the stress of labor (1, 2), there are apparently few reports

Abbreviations used are : TSH, thyroid stimulating hormone ; T_4, thyroxine ; T_3, triiodothyronine ; rT_3, reverse triiodothyronine ; FT_4I, free thyroxine index.

dealing with the pituitary body-thyroid gland system.

We studied the dynamics of the pituitary body-thyroid gland system of the mother and fetus immediately after normal delivery, and our findings are reported herein.

MATERIALS AND METHODS

Subjects included Japanese who had experienced a normal gestation and labor (without history of thyroid disease) and normal full-term babies who had had a normal neonatal period (14 cases).

Blood was collected from vena cubiti and umbilical artery of the mother immediately after labor. Sera were isolated immediately and stored at −20°C. Thyroid stimulating hormone, thyroxine, triiodothyronine, reverse triiodothyronine and ^{125}I-T_3-uptake were determined from the same sample. Determination was made of TSH, T_4, T_3 by radioimmunoassay using polyethylenglycol (Kaken Kagaku), of rT_3 by radioimmunoassay with double antibody (Dainabott Radioisotope Co.) and of ^{125}I-T_3-uptake with Thyopac-3 (Kaken Kagaku).

RESULTS

1. TSH Levels in Maternal Blood and Umbilical Arterial Blood

The maternal blood TSH level was 10.76±1.32 μu/ml and the umbilical arterial blood TSH at 10.16±2.41 μu/ml. TSH levels in maternal blood

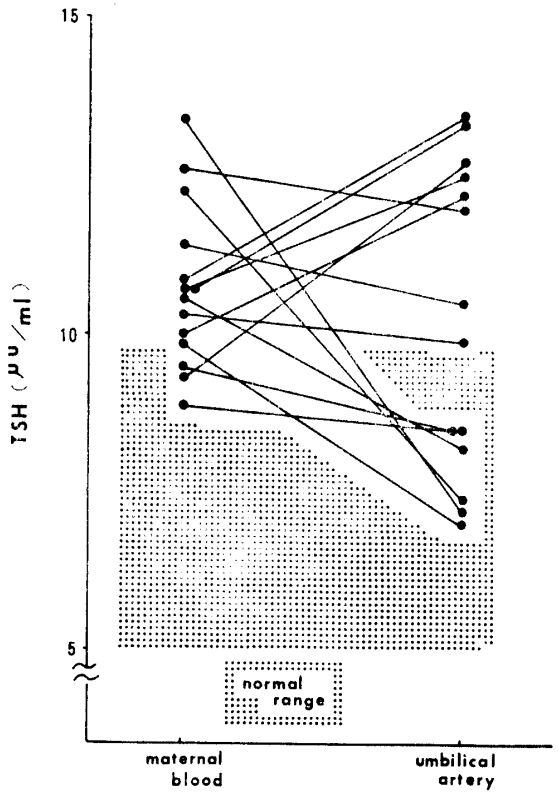

Fig. 1. Serum TSH concentrations in paired maternal blood and umbilical arterial blood specimens.

and umbilical arterial blood were higher than those in women with normal thyroid function.

There was no significant difference in TSH levels between maternal blood and umbilical arterial blood (Fig. 1).

2. T_4 Levels in Maternal Blood and Umbilical Arterial Blood

The maternal blood T_4 level was 14.25 ± 2.45 μg/dl and the umbilical arterial blood T_4 level 9.88 ± 0.69 μg/dl. The T_4 level in maternal blood was higher than that in the umbilical arterial blood and in women with normal thyroid function. The umbilical arterial blood T_4 level was within the limit for women with normal thyroid function (Fig. 2).

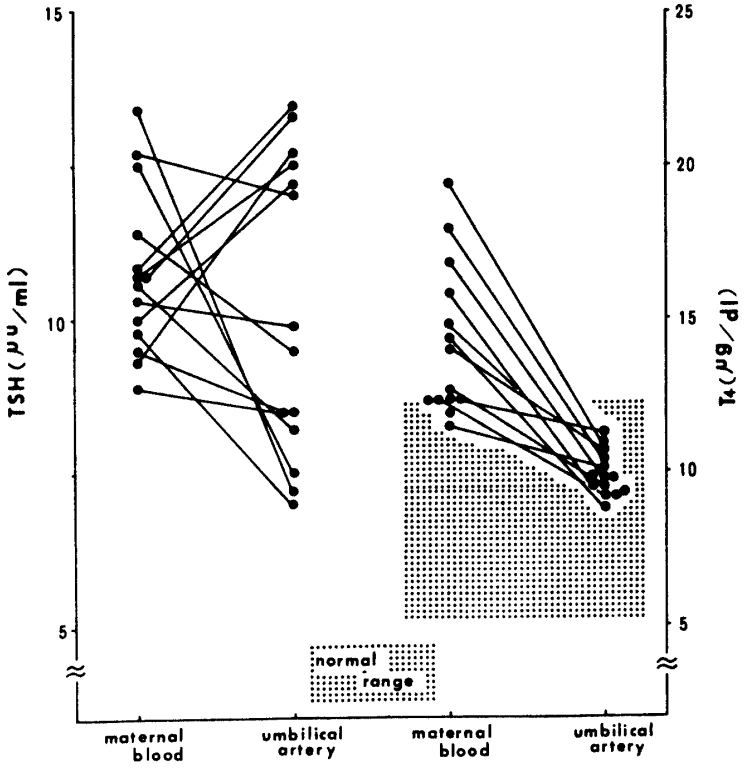

Fig. 2. Serum TSH and T_4 concentrations in paired maternal blood and umbilical arterial blood specimens.

3. Thyopac-3 Values in Maternal Blood and Umbilical Arterial Blood

The relative amount of T_4 concentration was studied by measuring the degree of unsaturation of thyroxine binding globulin (TBG) by T_4. The maternal blood Thyopac-3 value was $130.0\pm5.0\%$, being within the limit in cases of hypothyroidism. The umbilical arterial blood Thyopac-3 value was $107.3\pm7.8\%$ and within the limit for women with normal thyroid function (Fig. 3).

4. Free Thyroxine Index for Maternal Blood and Umbilical Arterial Blood

Free thyroxine index was obtained by dividing T_4 value by Thyopac-3 value.

Maternal blood FT_4I was 10.9 ± 1.96, showing higher values in many cases than in women with normal thyroid function. Umbilical arterial blood FT_4I

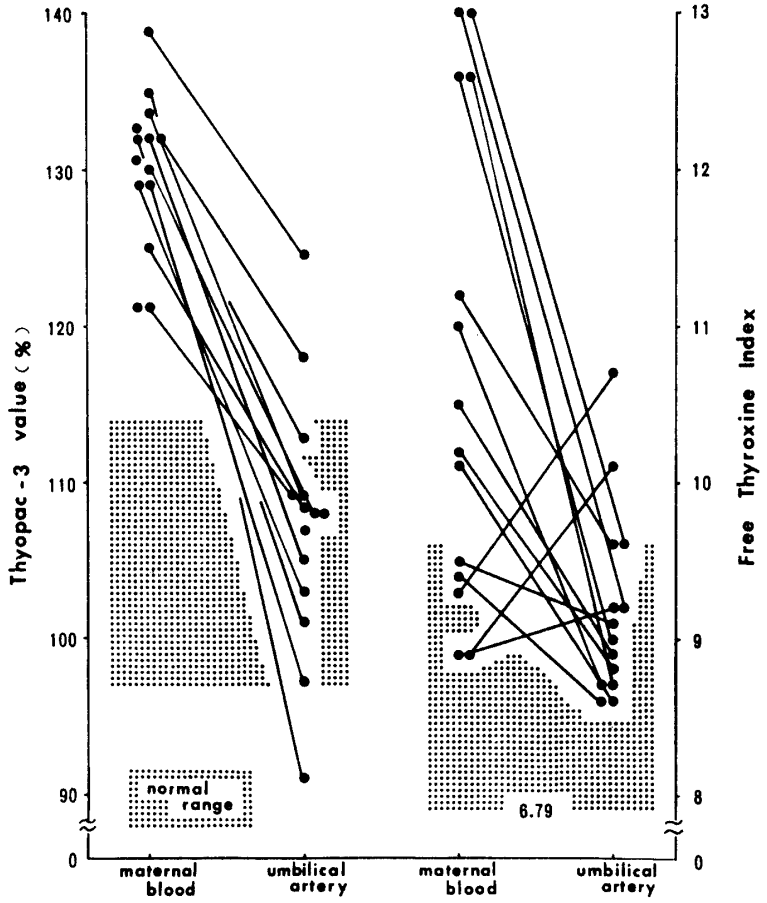

Fig. 3. The values of the Thyopac-3 and free thyroxine index in paired maternal blood and umbilical arterial blood specimens.

was 9.34 ± 0.52, this level being within the limit for women with normal thyroid function (Fig. 3).

5. T_3 Levels in Maternal Blood and Umbilical Arterial Blood

The T_3 level in maternal blood was 2.21 ± 0.38 ng/ml, while that in umbilical arterial blood was 0.81 ± 0.28 ng/ml.

The T_3 level in maternal blood was about 2.7 times that in umbilical arterial blood, these values being high compared with those for women with normal thyroid function. The umbilical arterial blood T_3 level was within the limit for women with normal thyroid function (Fig. 4).

6. rT_3 Levels in Maternal Blood and Umbilical Arterial Blood

The rT_3 level in umbilical arterial blood was 2.35 ± 0.29 ng/ml and that in maternal blood 0.78 ± 0.08 ng/ml. The rT_3 level in umbilical arterial blood was about three times that in maternal blood, and the rT_3 level in maternal blood also showed values higher than the limit for women with normal thyroid function, as determined by Chopara (3) (Fig. 5).

7. T_3/T_4, rT_3/T_4 Ratio in Maternal Blood and Umbilical Arterial Blood

T_3 and rT_3 are considered to be converted mainly from T_4 (3). Thus, the T_3/T_4, rT_3/T_4 ratio was used to study the degree of conversion from

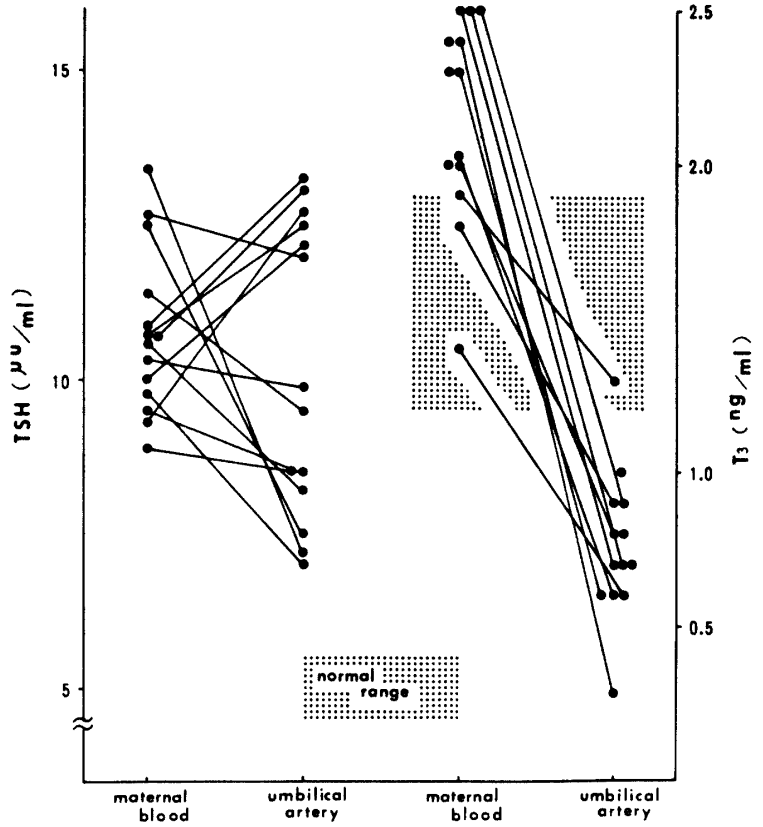

Fig. 4. Serum TSH and T_3 concentrations in paired maternal blood and umbilical arterial blood specimens.

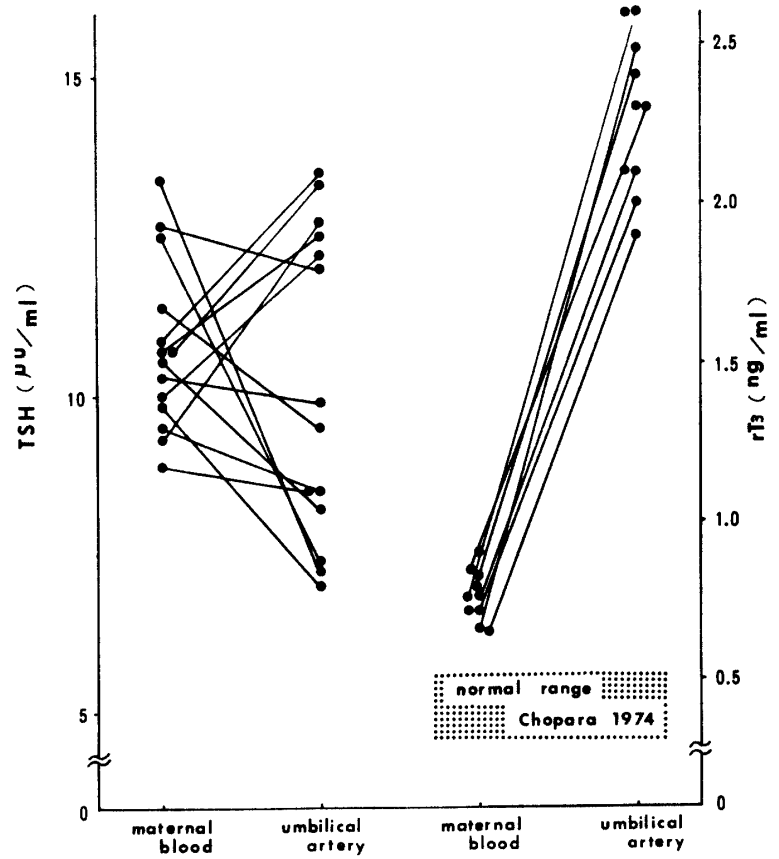

Fig. 5. Serum TSH and rT_3 concentrations in paired maternal blood and umbilical arterial blood specimens.

T_3 or T_4 to rT_3.

The T_3/T_4 ratio was 1.57 ± 0.29 in maternal blood and at 0.79 ± 0.23 in umbilical arterial blood. On the other hand, the rT_3/T_4 ratio was lower in maternal blood at 0.57 ± 0.11 than in umbilical arterial blood at 2.38 ± 0.45 (Fig. 6).

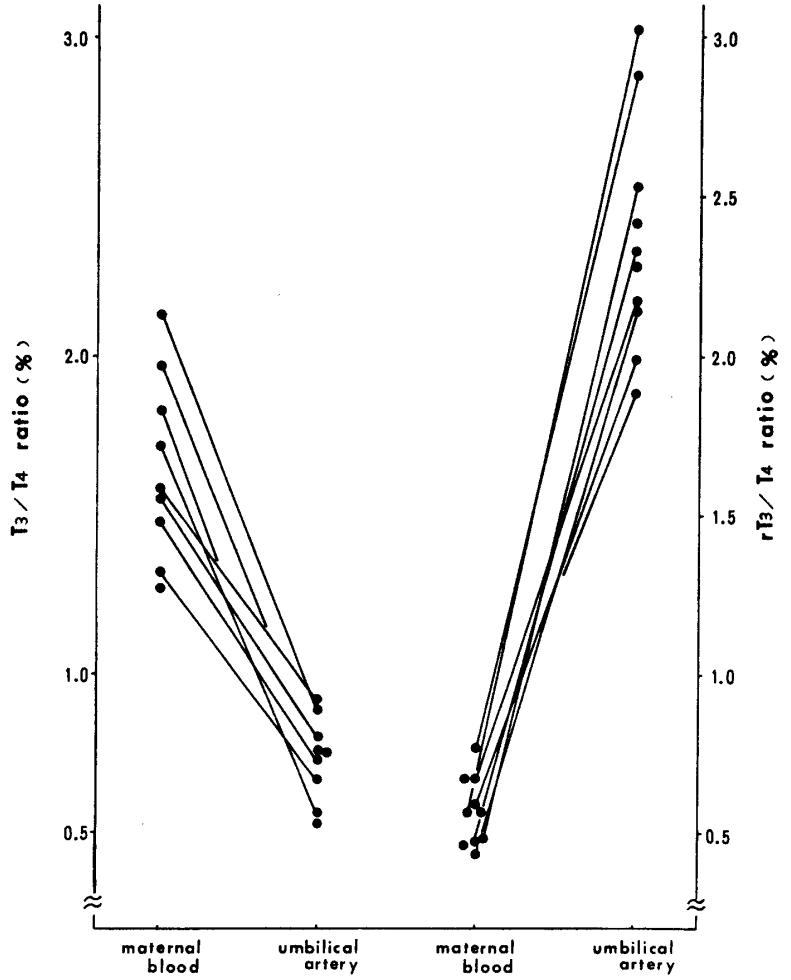

Fig. 6. Serum T_3/T_4 and rT_3/T_4 ratio in paired maternal blood and umbilical arterial blood specimens.

DISCUSSION

In the human fetus, TSH synthesis in the pituitary body has been confirmed (4) and TSH has been detected in fetal blood at around 12 weeks' gestation (5).

Meanwhile, the thyroid shows intra-epithelial plate at 8 weeks' gestation, formation of follicle and accumulation of colloid in follicle at the 12th week and completion of formation of follicle at the 19th week (6) ; blood thyroxine can be determined at 11 weeks' gestation (5).

Thus, it is surmised that the pituitary body-thyroid gland system of fetuses will acquire the structure and function almost completely at 19 weeks' gestation. Sakamoto *et al.* (6) administered TRH to the mother in cases of

therapeutic abortion at the second trimester of pregnancy and demonstrated that the fetal pituitary body at 20 weeks' gestation responds to TRH passing through the placenta.

These same workers examined changes in maternal and fetal TSH, thyroxine and free thyroxine in the course of gestation. They injected ^{131}I-T_3, ^{131}I-T_4 100μCi into the mother in the latter period of pregnancy, and examined the transfer to maternal blood after 24 hours. The transferring level was very scanty and they reported that the pituitary body-thyroid gland system of fetuses functions independently of the mother from the middle period of gestation.

Fisher *et al.* (7) reported that TSH value on delivery was higher in umbilical arterial blood with 8.9 ± 0.93 μu/ml than in maternal blood with 4.3 ± 0.40 μu/ml. According to our own finding there was no significant difference between maternal blood and umbilical arterial blood, both levels showing high values compared with the report of Fisher *et al.* (7).

The TSH value in umbilical arterial blood was higher than that in women with normal thyroid function and TSH did not pass through the placenta. It therefore appears that the fetal pituitary body would function independently of the mother and would be in a state of hypersecretion of TSH.

It is considered that blood T_4 is combined first with thyroxine binding globulin (TBG), and then with thyroxine binding prealbumin (TBPA) (8) and that more than 99.9 per cent of T_4 combines with protein.

Accordingly, the T_4 level increases or decreases with a change in the TBG binding capacity (9).

To determine the influence of TBG, we used Thyopac-3 to study the relative amount of T_4 concentration by measuring the degree of unsaturation of TBG by T_4.

The maternal blood Thyopac-3 value, unlike T_4 concentration, was less than that of women with normal thyroid function, that is, within the limit of hypothyroidism.

In pregnant women, the TBPA binding decreases while the TBG binding capacity increases, and thus it has been reported that the increase in T_4 is affected strongly by TBG (10).

It is therefore possible that the increase in TBG with an increase in estrogen has a potent influence on the total T_4 concentration and Thyopac-3 value.

Clark and Brown (11) maintained that a value obtained by multiplying PBI by the ^{131}I-resin uptake rate is an index capable of avoiding the influence of thyroxine binding protein, reflects the thyroid function more correctly and parallels free thyroxine. They designated it as the free thyroxine index (FT_4I).

Based on the same concept, we divided the total T_4 value by Thyopac-3 value and designated the value obtained as FT_4I.

The FT_4I value in maternal blood, unlike Thyopac-3 value, was higher than that of women with normal thyroid function, while the FT_4I value in umbilical arterial blood was within the limits of normal thyroid function.

Accordingly, we presumed that TBG would increase in excess of an increase in maternal blood T_4 on delivery and consequently that the unsaturated part of TBG would increase.

As to free T_4 which actually has hormonal activity, Sakamoto *et al.* (6) reported that fetal free T_4 atood at 2.24 ± 0.13 ng/dl, this values being almost equal to maternal free T_4.

Fisher *et al.* (7) reported that fetal free T_4, 2.91 ± 0.1 ng/dl was higher than maternal blood free T_4, 2.3 ± 0.13 ng/dl.

Although we did not determine free T_4 directly it was assumed from results of FT_4I that free T_4 would probably be higher in maternal blood.

The T_3 level in maternal blood was about 2.7 times that in umbilical arterial blood, and it was higher than that in women with the normal thyroid function.

On the other hand, the T_3 level in umbilical arterial blood is lower than that in women with the normal thyroid function and is within the limit in cases of hypothyroidism.

Fisher *et al.* (7) also reported high values for the T_3 level in maternal blood. Hotteling and Sherwood (12) made a simultaneous measurement of TBG, reporting that the T_3 value, like the T_4 value, was affected by the change of TBG, increased during the course of pregnancy and reached a peak during labor.

It was also reported that the T_3 level in umbilical arterial blood was markedly low but that the T_3 level had been low in the fetal period and remained low until immediately after birth (13, 14).

Erenberg *et al.* (15) reported that the T_3 level was 0.50 ng/ml immediately after birth and increased sharply to 2.93 ng/ml one hour after.

With the recent development of RIA for reverse T_3, which is produced mainly by conversion of T_4 as is T_3 and which has no thyroid hormone action because of a slight structural difference — the difference in the iodine binding site at only one place (3) and also with the reverse T_3 level showing high value in fetuses (3), the significance of rT_3 at labor has attracted much attention.

The rT_3 level in umbilical arterial blood is about three times that in maternal blood. The rT_3 level in maternal blood was also higher than the limit for women with normal thyroid function, as determined by Chopara (3).

According to a report by Mizuno *et al.* (16), the rT_3 level was low both in maternal and umbilical arterial blood but showed similar fluctuations, compared with our results.

T_3 and rT_3 are secreted in part from the thyroid gland. In adults, however, 40 to 70 per cent of blood T_3 is considered to be produced by conversion from T_4 in the peripheral tissue ; and about that much rT_3 is considered converted (17). Thus, the degree of conversion was studied by the T_3/T_4, rT_3/T_4 ratio.

The maternal blood T_3/T_4 ratio was higher than the umbilical arterial blood T_3/T_4 ratio, while the maternal blood rT_3/T_4 ratio was lower than the

umbilical arterial blood rT_3/T_4 ratio.

Thus, it was presumed that conversion from T_4 to T_3 with potent biological activity would also be active in the mother and that conversion from T_4 to rT_3 with no biological activity would be active in the fetus.

The fact that the T_3 value and T_3/T_4 value are low in the fetus is presumed to be due to the conversion rate from T_4 to T_3 being low. Sakamoto *et al.* (6) assumed that the lack of activity of conversion enzyme from T_4 to T_3 would be accountable for the low conversion rate.

Considering that the activity of T_3 has recently attracted attention, they reported that this phenomenon might be an intricate mechanism to inhibit unnecessary metabolism to some extent.

Accordingly, biologically inactive rT_3 and high rT_3/T_4 values may be the result of the participation of rT_3 and rT_3/T_4 in this mechanism.

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