Effect of perinatal asphyxia on thyroid hormones

Denise N. Pereira,¹ Renato S. Procianoy²

Abstract

Objective: to verify the effect of perinatal asphyxia on thyroid hormone levels in term newborn infants.

Methods: we carried out a case-control study with 17 term and asphyxiated (A) and 17 term and control (N) newborn infants at the Hospital de Clínicas de Porto Alegre. Patients were paired according to color of skin, sex, type of delivery, gestational age, and weight at birth. We collected umbilical cord plasma T4, T3, free T4, reverse T3, and TSH after 18 to 24 hours of life and from asphyxiated and control newborn infants.

Results: there were no differences in thyroid hormones of cord blood, with the exception of reverse T3, which was higher in A than in controls [median (25th-75th percentile): A= 2(1.4-2); N= 1.41 (1.13-1.92); P=0.037)]. Thyroid hormone levels were lower in A than in controls on samples collected within 18-24 hours after birth, except for reverse T3, which was similar in both groups [average ± SD: T4 A= 9.79 ± 2.59; N=14.68 ± 3.05; P=0.001; median T3 A= 40.83 (37.4-80.4); N= 164 (56.96-222.5); P=0.003; average ± SD: free T4 A=1.85 ± 0.92; N= 2.8 ± 0.74; P=0.004; median: reverse T3 A=1.54 (1.16-1.91); N=1.31(0.87-2); P=0.507; TSH A=9.1 (6.34-12.95); N=14.5(12.9-17.85); P=0.008].

Conclusions: our data suggest that lower T4, free T4, and T3 levels are secondary to lower TSH levels in asphyxiated newborns; also, peripheral metabolism of T4 in asphyxiated infants can be altered due to low T3 and normal reverse T3 levels.


Perinatal asphyxia provokes multiple alterations in the body due to failures in the gas exchange system. Among these alterations we find hypoxia, hypercapnia, and decrease of blood pH, thus causing redistribution of the blood flow from less vital organs to vital organs such as the brain, heart, and adrenal glands.¹

Asphyxia also triggers a rapid increase in the secretion of some hormones, such as catecholamines,² glucocorticoids,²-⁴ ACTH,⁴ beta-endorphins,⁴ antiidiuretic hormone,⁵-⁸ aldosterone,¹²,9,10 renin¹¹ and atrial natriuretic peptide,⁹,¹² as well as a reduction in insulin.¹

There are few studies evaluating the effect of perinatal asphyxia on thyroid hormones,¹³-¹⁶ with conflicting results. The action of these hormones on the synthesis of mitochondrial enzymes and structural elements is extremely important, in addition to participating in thermogenesis, water and electrolyte transportation, and in the growth and development of the central nervous system and skeleton. Low levels of thyroid hormones in nonthyroidal illnesses are associated to poor prognosis.¹⁷ This study aims at comparing T4, T3, free T4 (FT4), T3 reverse (rT3), and TSH plasmatic concentrations in the cord blood of term newborns, asphyxiated or not, and in newborns with 18-24 hours of life.

Patients and methods

The study population consisted of full-term newborns, with 1- and 5-minute Apgar scores < 7 and umbilical vein
blood pH <7.2, sequentially born until a total of 17 asphyxiated newborns. We included as control the first normal full-term newborn with 1- and 5-minute Apgar scores greater than or equal to 8 and umbilical vein blood pH greater than or equal to 7.2, born after the asphyxiated newborn who had similar birth weight, gestational age, type of delivery, color and sex.

Those newborns with any sort of malformation or congenital disease, or those whose mothers had any disease or were treated with antihypertensive, diuretic, corticosteroid, or antithyroid drugs were excluded from the study. Gestational age was evaluated according to obstetric gestational age and confirmed by physical examination. When the difference between obstetric gestational age and clinical evaluation was higher than 2 weeks, clinical evaluation was considered. Newborns were classified as small, big, or appropriate for gestational age, based on intrauterine growth curves.

Immediately after birth, umbilical cord was clamped in two different points, and a blood sample was collected for venous blood gas analysis and determination of T4, T3, FT4, rT3, and TSH. Eighteen to 24 hours after birth, following the example of Borges et al., a blood sample was collected for arterial blood gas analysis and dosage of thyroid hormones of each newborn in both groups.

All the asphyxiated newborns were admitted to an intensive care unit, had control of diuresis during 24 hours and received parenteral hydration. None of the asphyxiated newborns was fed during the study period. The controls were healthy newborns, who received assistance in the same lodging and who were fed on demand.

T4, T3, FT4, and TSH were measured by radioimmunoassay with a Coat a Count kit. rT3 was dosed with reverse T3 kit, also by the radioimmunoassay method.

The values of FT4 and T3 were expressed in ng/dl, TSH in mU/ml, those of total T4 in mg/dl, and those of rT3, in ng/ml.

The sample size was calculated considering a significance of 0.05 and a statistical power of 90% to detect a difference of 1.33 in the FT4 level between the two groups, based on the data presented by Borges et al. The calculated sample size was 14 newborns in each group. Continuous variables were described through means, medians, and standard deviations, and the categorical variables were described through the proportion of the data obtained from the sample. In the analysis, we used the chi-square or Fisher’s exact tests for categorical variables. In order to assess continuous variables, we used Student’s t test or Wilcoxon test for pair-matched samples.

This study was approved by the Committee on Ethics of the Hospital de Clínicas de Porto Alegre. A verbal and written term of consent was obtained from the newbornt’s parents or guardians.

### Results

There were no differences between the groups concerning gestational age (39.2±0.9: 39.3±1.2 weeks: asphyxiated and non-asphyxiated, respectively), birth weight (3,178.5±653.4: 3,238.5±362.7 grams: asphyxiated and non-asphyxiated, respectively), sex (12/5: F/M in each group), ratio AGA/BGA (15/2 in each group), type of delivery (14/3: vaginal/cesarean in each group) and color (14/3: white/non-white in each group). The group of asphyxiated newborns presented significantly lower 1- and 5-minute Apgar scores. In cord blood, pH and base excess were significantly lower and pCO2 was significantly higher. We found that pO2 was lower in this group, but this difference was not statistically significant (Table 1). Means for T4, T3, FT4, and TSH were similar in both groups; the mean for rT3 was significantly higher in the asphyxiated group (Table 2).

#### Table 1 - Apgar score and biochemical indices in umbilical cord blood

<table>
<thead>
<tr>
<th></th>
<th>Asphyxiated n=17</th>
<th>Non-asphyxiated n=17</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-minute Apgar</td>
<td>1 (0-1)</td>
<td>9 (8-10)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>5-minute Apgar</td>
<td>3 (1-5)</td>
<td>10 (9-10)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>pH</td>
<td>6.98±0.17</td>
<td>7.32±0.07</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PCO2</td>
<td>68.3±28.2</td>
<td>38.9±7.4</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>PO2</td>
<td>22.1±11.3</td>
<td>30.2±8.5</td>
<td>0.065*</td>
</tr>
<tr>
<td>Base excess</td>
<td>-15.3±6.9</td>
<td>-4.43±3.2</td>
<td>0.001§</td>
</tr>
</tbody>
</table>

Values expressed in mean± standard deviation or median (25th-75th percentiles)
* Student t test for pair-matched samples
§ Wilcoxon test for pair-matched samples

We were not able to verify differences among the means for pH, pCO2, and base excess in the blood collected from the newborn with 18-24 hours. However, pO2 was significantly higher in the group of asphyxiated babies (Table 3). There was significant difference among T4, T3, FT4, and TSH means between the two groups, with lower means for the asphyxiated group. The mean for rT3 was similar in both groups (Table 4).

#### Table 2 - Plasma concentration of thyroid hormones in umbilical cord blood

<table>
<thead>
<tr>
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<th>Asphyxiated n=17</th>
<th>Non-asphyxiated n=17</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4(mg/dl)</td>
<td>11.2±4.19</td>
<td>10.4±3.22</td>
<td>0.453*</td>
</tr>
<tr>
<td>T3(mg/dl)</td>
<td>68 (44.2-173.7)</td>
<td>62.5(41.8-90.3)</td>
<td>0.619§</td>
</tr>
<tr>
<td>FT4(mg/dl)</td>
<td>1.37±0.59</td>
<td>1.36±0.24</td>
<td>0.951*</td>
</tr>
<tr>
<td>rT3(mg/ml)</td>
<td>2 (1.4-2)</td>
<td>1.4 (1.1-1.92)</td>
<td>0.037§</td>
</tr>
<tr>
<td>TSH(mU/ml)</td>
<td>14(1.7-2-31.1)</td>
<td>10(2.7-12.1)</td>
<td>0.07§</td>
</tr>
</tbody>
</table>

Values expressed in mean± standard deviation or median (25th-75th percentiles)
* Student t test for pair-matched samples
§ Wilcoxon test for pair-matched samples
Table 3 - pH and blood gases in the blood of newborns with 18-24 hours of life

<table>
<thead>
<tr>
<th></th>
<th>Asphyxiated n=17</th>
<th>Non-asphyxiated n=17</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.39± 0.08</td>
<td>7.45± 0.06</td>
<td>0.082*</td>
</tr>
<tr>
<td>PCO₂</td>
<td>28.3± 4.98</td>
<td>27.5± 5.6</td>
<td>0.669*</td>
</tr>
<tr>
<td>PO₂</td>
<td>109.4± 51.5</td>
<td>72.6± 16.6</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Base excess</td>
<td>-5.43± 5.37</td>
<td>-3.6± 2.4</td>
<td>0.366</td>
</tr>
</tbody>
</table>

Values expressed in mean± standard deviation or median (25th-75th percentiles)

* Student t test for pair-matched samples
§ Wilcoxon test for pair-matched samples

Discussion

Several agents intervene with the thyroid function, acting on several stages of its metabolism. The effect of hypoxia on thyroid hormones has been long recognized. In animals, hypoxia reduces thyroid function and extrathyroidal metabolism of T4.20 Similarly, Moshang et al.21 found an increase in the levels of rT3 in patients with acute hypoxemia, suggesting a reduction in its degradation. In the same study, patients with chronic hypoxemia showed decreased levels of T3, and increased rT3 levels, revealing alterations in extrathyroidal metabolism.

There are few studies on the effect of perinatal asphyxia on thyroid hormones and the available studies present conflicting results, probably related to methodological differences.13-16

In our study, the matching of cases and controls provided us with two similar series, in which the greatest difference among newborns was related to asphyxiation and non-asphyxiation. Moreover, the pair-matched case-control study reduced the probability of confounding biases by neutralizing the influence of several factors, such as sex, gestational age, weight, color, and type of delivery, on hormone levels. The groups showed differences to whether or not they received enteral nutrition. However, the nutrition variable does not cause impact on hormonal levels provided malnutrition is not present.22

In cord blood, the values for pH, base excess, and pO₂ means were lower and the values for pCO₂ were higher in the group of asphyxiated newborns, as expected. All the differences were statistically significant, except for pO₂. Within the 18-24 hours of life, there were no differences between the two groups in terms of the values obtained through gas analysis, except for pO₂, which was higher in the group of asphyxiated newborns. This increased value was certainly due to the use of supplementary oxygen and/or mechanical ventilation in this group, with the highest oxygen supply.

The means for thyroid hormones, in cord blood, were similar in both groups, except for rT3, which was higher in the group of asphyxiated newborns. This result resembles those obtained by Borges et al.,13 who did not find differences in the concentration of FT4 and FT3 in cord blood, and those presented by Franklin et al.,15 which did not find statistical differences in the concentration of T4, T3, rT3, FT4, TBG, and TSH between normal and asphyxiated newborns.

The increase of rT3 observed in cord blood may indicate an alteration in the peripheral metabolism of thyroid hormones through the inhibition of 5'-deiodinase activity, which is similar to what occurs in acute hypoxia.21

On the other hand, in newborns with 18-24 hours of life, lower levels of T4, T3, FT4, and TSH were observed in asphyxiated newborns, in which the basal levels (in cord blood), with exception of FT4, failed to increase. Borges et al.13 found that FT4 and FT3 levels failed to increase within the first 48 hours of life in the group of asphyxiated newborns, even though their TSH levels were normal.

Alterations in thyroid hormone metabolism due to nonthyroidal illnesses are known as euthyroid sick syndrome.23-25

The typical pattern of the euthyroid sick syndrome includes a reduction in T3 concentration and an increase in rT3 concentration, with a suppressed response of TSH to TRH and only a minimum tendency towards a reduction in serum T4 and TBG levels.22 The level of involvement of the thyroid function is correlated with the severity of the disease, and the prognosis gets worse with the reduction of hormone levels,15,22,24

The characteristics of this syndrome have been described in several situations, such as protein-energy malnutrition,26 postoperative period of large surgeries,24 sepsis,15 meconium aspiration,15 and asphyxia.13 This syndrome is also associated with the use of certain drugs, such as corticosteroids,25,27-29 dopamine,27-29 iodized contrasts,25,27-29 among others.

The difference in the behavior of FT4 and TSH found in our study and in that conducted by Borges et al.13 may be the consequence of multiple alterations that result from this syndrome.23-25

Table 4 - Plasma concentration of thyroid hormones in asphyxiated and non-asphyxiated newborns with 18-24 hours of life

<table>
<thead>
<tr>
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<th>Asphyxiated n=17</th>
<th>Non-asphyxiated n=17</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4(m g/dl)</td>
<td>9.79± 2.6</td>
<td>14.7± 3.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>T3(ng/dl)</td>
<td>40.8(37.4-80.4)</td>
<td>164(57-222.5)</td>
<td>0.003*</td>
</tr>
<tr>
<td>FT4(ng/dl)</td>
<td>1.85± 0.92</td>
<td>2.8± 0.74</td>
<td>0.004*</td>
</tr>
<tr>
<td>rT3(ng/ml)</td>
<td>1.54(1.2-1.9)</td>
<td>1.3(0.87-2)</td>
<td>0.507*</td>
</tr>
<tr>
<td>TSH(m U/ml)</td>
<td>9.1(6.34-12.9)</td>
<td>14.5(12.9-17.8)</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

Values expressed in mean± standard deviation or median (25th-75th percentiles)

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§ Wilcoxon test for pair-matched samples
We conclude that there are differences in the plasma concentration of T4, T3, TSH, and FT4 of asphyxiated newborns; however, these differences are less pronounced in this group. Alterations in hormone production and in the peripheral metabolism of T4 may be responsible for these differences, since we found low levels of T3 in contrast to normal levels of reverse T3.

Central hypothyroidism is the most common alteration found within the first 24 hours, where low levels of thyroid hormones are secondary to low TSH concentration. We were not able to determine the duration and extension of these alterations in the metabolism of asphyxiated newborns, since this would lead to an ethical restriction, requiring several collections during several days, both in asphyxiated and control newborns.

The importance of thyroid hormones to the normal development of the brain and intellectual function, and their relation with patients’ prognosis requires follow-up studies that correlate hormonal alterations with the occurrence of neurological sequelae. Studies that evaluate the role of T4 and/or T3 restoration in patients with subnormal hormonal levels should also be considered.

References


