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The evaluation of thyroid function in neonates according to gestational age

Thyroid hormones are important for stimulation of growth and development of various tissues including the central nervous system. Thyroid function abnormalities are among the factors that have been associated with poor neurodevelopmental outcome, especially in preterm and very low birth weight (VLBW) neonates. In these children the thyroid axis is immature, with reduced hypothalamic thyrotropin-releasing hormone (TRH) secretion, an immature response of the thyroid gland to thyrotropin (TSH), an inefficient capacity of the follicular cell to concentrate iodine and synthesize and iodinate thyroglobulin as well as a low capacity to convert tetraiodothyronine (T_4, thyroxine) into active 3,5,3'-triiodothyronine (T_3) (3). After preterm birth, total T_4 (TT_4), free T_4 (FT_4) and free T_3 (FT_3) levels remain lower than in term infants for the first weeks, particularly in preterms with respiratory distress syndrome and low Apgar score. For brain development, sufficient circulating FT_4 and not total T_4 is necessary for local intracellular T_3 production. Low FT_4 and FT_3 levels are strongly associated with higher mortality and severity of lung disease (1, 6, 8). Low FT_4 plasma levels during the first four weeks after birth in neonates born at less than 30 weeks gestation are associated with worse cognitive and neuromotor outcome at 5 years of age, but there is no evidence that thyroid hormone supplementation improves neurodevelopmental outcome of preterm infants (9). There is also no evidence, that thyroid hormone supplementation is not required in preterm infants with low plasma FT_4 levels, but efficient treatment protocol was not yet established (8). There are also no universally accepted protocols for the evaluation of thyroid status in premature infants. The normal range for free T_4 levels for preterm infants was not yet established (8). Mean free T_4 values in very preterm infants seem to be in the normal range for adult free T_4, but lower than in term infants (1).

The aim of our study was to assess the serum thyroid hormone concentrations in premature infants in the first six weeks of postnatal life according to gestational age.

MATERIAL AND METHODS

The study was conducted at the University Children's Hospital in Lublin in 2003–2004. The investigated group was composed of 116 neonates that were treated in Neonatal Intensive Care Unit and in Department of Neonates', Infants Pathology and Cardiology. Among children 88 were premature: 42 of 23 to 33 weeks' gestation and 46 of 34–37 weeks' gestation. The prematurity was associated with a variety of disorders, including perinatal depression, sepsis, pneumonia, respiratory distress syndrome or retinopathy. Inclusion criteria were absence of congenital abnormality, and maternal endocrine disease. The control group comprised 28 term neonates. Apgar scores at 1 minute were lowest in most immature infants. Table 1 gives the descriptive data for the groups.

Table 1. Gestational age, birth weight and Apgar score of investigated newborns

Group	Average gestational age (weeks)	Birth weight (g)	Apgar score
Preterm < 33 weeks (n= 42)	29.4 ± 2.67	1422 ± 419	5.4 ± 1.96
Preterm 34-37 weeks (n = 46)	35.6 ± 1.06	2822 ± 421	7.9 ± 1.80
Term neonates (n = 28)	38.9 ± 0.99	3347 ± 477	8.5 ± 1.43

Table 2. Mean thyrotropin (TSH) and thyroxine (T_4) serum concentrations in neonates in relation to gestational age

Group	Average chronological age (weeks)	TSH (mU/l)	FT_4 (pmol/l)
A. Preterm < 33 weeks (n= 42)	3.7±2.3	2.51 ± 2.14	11.05 ± 5.14
B. Preterm 34-37 weeks (n = 46)	3.6.±2.2	3.08 ± 1.82	15.93 ± 5.52
C. Term neonates (n = 28)	3.3±2.4	3.59 ± 3.11	18.37 ± 8.99
A vs B (p value)	n.s.	0.03	0.001
A vs C (p value)	n.s.	0.05	0.004
B vs C (p value)	n.s.	n.s.	n.s.

Blood samples were collected in the morning, during first six weeks after birth. The mean chronological age of children (since birth to examination) shows Table 2. As the quantity of serum was relatively small, only TSH and FT_4 were analyzed using ELISA method. The distribution of studied data sets were checked up by Kolmogorov-Smirnov test. Statistical analysis was performed with U Mann-Whitney test, $p < 0.05$ was regarded as statistically significant.

The study protocol was approved by the Ethics Committee of Medical University of Lublin.

RESULTS

Table 2 gives mean serum TSH and FT_4 levels in the investigated children in relation to gestational age. Results suggest that the higher the gestational age, the higher the hormone concentrations. The levels of TSH and FT_4 in preterms of less than 33 weeks were significantly lower than in other groups. The levels of hormones in 34–37 weeks preterms were lower than term neonates, but the difference was not statistically significant.

DISCUSSION

Thyroid deficiency during the latter two thirds of gestation and the first months after birth can result in mental retardation and sometimes neurological deficits (7). Materno-fetal transfer of thyroid hormones has been demonstrated in early fetal life. Very preterm newborns suddenly lack the maternal hormone contribution at a time when maturation of the hypothalamo-pituitary-thyroid system and thyroid hormone metabolism has not been completed. Thus transient hypothyroxinemia is observed in the majority of infants younger than 30 weeks' gestation (5). Our studies

have shown that TSH and FT_4 concentrations in the group of newborns younger than 33 weeks' gestation are much lower than in infants born at term or nearly term. The maturation of the thyroid hormone metabolism reflected by increase in hormone concentration with gestational age was observed. This association between gestational age and higher thyroid hormone concentrations has been shown previously in first 14 days of life of very preterm infants (1). Our results are similar and suggest that the abnormalities of thyroid function may persist at least 6 weeks. Low thyroid hormone concentrations were found in the preterms below 33 weeks' gestation, with low birth weight and low Apgar score (2). Low free thyroxine levels were accompanied by lower TSH levels, which probably reflects the immaturity of the hypothalamic-pituitary gland-thyroid axis and weak infant's response to severe illness (4).

It is not clear what critical FT_4 concentrations in plasma are below which the risk of impaired neurodevelopment increases. Probably, the cut off value below which the thyroid hormone supplementation must be installed, differs according to gestational and postnatal age. It is suggested that the incidence of transient hypothyroidism (low T_4 and high TSH) in the premature and VLBW infants (1 in 250) is higher than in term infants (1 in 3,500). This disorder is even more common in sick preterm infants, particularly those requiring intensive neonatal care (5%); with congenital defects, treated with dopamine and amiodarone or after iodine exposure (2, 4). Thus the problem seems to be important for the improvement of the clinical and neurodevelopmental outcome of the very preterm infants.

CONCLUSIONS

Further studies are needed to elucidate the significance of the thyroid function abnormalities in very preterm infants. Most of all the proposals of protocols for the evaluation of thyroid function in preterm infants are needed.

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SUMMARY

The thyroid function in neonates in first six weeks of postnatal life according to gestational age has been studied. The levels of TSH and FT_4 in preterms of less than 33 weeks were significantly lower than in 34–37 weeks' preterms or term neonates. Further studies are needed to elucidate the thyroid function abnormalities in very preterm infants and to establish the appropriate method of proceeding.

Ocena czynności tarczycy u noworodków w zależności od wieku płodowego

Celem pracy była ocena stężenia hormonów tarczycy (TSH i FT_4) u noworodków w pierwszych sześciu tygodniach życia w zależności od wieku płodowego. Wykazano, że u wcześniaków urodzonych przed 33 tygodniem ciąży stężenia hormonów są istotnie niższe niż u noworodków urodzonych między 34 a 37 tygodniem i noworodków donoszonych. Opracowanie wytycznych odnośnie do leczenia substytucyjnego wcześniaków wymaga dalszych badań.