Deficiency of Thyroid Hormones in Pregnancy and in Newborn

Epidemiologic Etiopathogenic and Clinical Aspects

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Abstract

Objective: *Assessment of the iodine deficiency în the pregnant woman, în the newborn, the prevalence of hypothyroidism, and the dynamic of this affection în the period 2002-2008.*
Method: *A representative national multicentric study group of 1976 pregnant women and 969 newborn was assessed for the prevalence of hypothyroidism and the dynamic of this affection în the period 2002-2008. The multicentric study of transversal descriptive epidemiologic type was made on a probabilistic representative sample for the country. Were assessed the newborn included în the National Program of neonatal screening (approximately 70000 newborn per year); etiopathogenic aspects of the congenital hypothyroidism (study made on 40 children with congenital hypothyroidism). Neonatal TSH samples were obtained through the dry spot method and the clinic exam was performed în children with congenital hypothyroidism.*
The urinary iodine în blood was assessed în pregnant women hospitalized for birth în the same observation period. Those women were questioned based on a questionnaire în the post-partum period and measured for the mother's blood level of TSH, indicator of the iodine level.
Results: *This study shows a deficiency within the limits of small deficiency în the pregnant women and average în the newborn; the prevalence of the congenital hypothyroidism is 1/4000-1/7000 newborn, decreasing from 2002 until 2008; 2,8% from the newborn presented transitory hypothyroidism; the outcome of the iodine deficiency on the newborn includes low birth weight, and the newborn thyroidian pathology is frequently associated.*
Conclusions: *Interdisciplinary collaboration is necessary and the inclusion of prenatal examination determinating the iodine concentration is useful, and also the post-screening of the congenital hypothyroidism. The complexity of the etiology and of the consequences of the thyroid hormone deficiency recommends the screening programs for congenital hypothyroidism*
Keywords: *screening, congenital hypothyroidism, TSH*

Introduction

The thyroid hormones are indispensable for the organism development right from the intrauterine life. In the first three months of the intrauterine development the necessary thyroid hormones are provided by the maternal hormones, and afterwards, at around 10-11 weeks of breeding the fetal thyroid being capable of the proper synthesis of the thyroid hormones[1,2,3,4].

The thyroid hormone deficiency of the mother during the pregnancy generates pathologic conditions that turn out in abortion, premature birth and in what regards the foetus, low weight at birth, disorders in the psychointellectual development. A deficient synthesis of the hormones by the fetal thyroid generates serious neuropsychic disorders that manifests from the first postnatal months, a physiopathologic condition also known as congenital hypothyroidism.

Considering the plurifactorial etiology of the thyroid hormone deficiency with impact on the development of the foetus and of the new born and the importance of the precocious control of thyroid deficiency, this study has as main objectives:

- The evaluation of the iodine deficiency in the pregnant woman, possible condition of the psychointellectual development disorders of the child, representative study made on 1976 pregnant women;
- The evaluation of the iodine deficiency in the newborn, national study on 969 newborn;
- The evaluation of the prevalence of hypothyroidism and the dynamic of this affection in the period 2002-2008, study made on the newborn included in the National Program of neonatal screening (approximately 70000 newborn per year);
- Etiopathogenic aspects of the congenital hypothyroidism (study made on 40 children with congenital hypothyroidism).

Starting with 1990, The Institute for the Protection of the Mother and the Child "Alfred Rusescu", with technical and financial support from the UNICEF Representation, deployed a series of projects that aimed at the nutrition of the child, paying attention including to the intrauterine life[3,4].

Work methodology

The conception of execution and data sources

The study was made on the basis of the determination of the neonatal TSH through the dry spot method and the clinic exam in children with congenital hypothyroidism, in the period 2002-2008. The study of transversal descriptive epidemiologic type was made on a probabilistic sample of representatives for the entire country.

The urinary iodine in blood was dosed on pregnant women hospitalized for birth in the same observation period. Those women were questioned based on a questionnaire in the postpartum period. All these mother's newborn had a blood sample taken for the determination of the level of TSH, indicating the iodine level.

Sample and sampling

The "cluster" technique was used in order to obtain a representative sample of pregnant women, among the women hospitalized for birth in maternity clinics, in the period of observation. This sample is representative at national level, the margin of error being +/- 3% and a confidence of 95%.

For the selection of the pregnant women, the following procedure was applied:

- the 42 counties of Romania, including the Bucharest Municipality and the Ilfov county, were grouped in 11 regions, in function of geo-demographic similitudes;
- from each region two counties were selected at random, respectively 2 sectors for Bucharest;
- from each county/sector all the maternity clinics were taken - both in urban and rural environment - existent on the county territory;
- from these maternity clinics all the pregnant women hospitalized for birth were selected, in a determined interval of 7 days, the same for all the counties.

Eligibility

In the study were included the women in at least 28th week of pregnancy and who presented at least one of the labour signs: contractions, plain cervix, film broken. The study also included the pregnant women scheduled for Caesarian operation, upon request.

The study didn't include women who had been in contact with iodine, in order not to distort the iodine test. Also included in the study were all the newborn of these pregnant women that became mothers. Eventually, a sample of 1595 pregnant women/mothers and just as many babies was obtained.

Procedures and work methods

The study was made with the support of the public health directions (DSP), of the Universities of Medicine and Pharmacy, of the managements of the medical units selected, as well as of the professionals from the obstetrics and newborn sections.

The data was collected simultaneously by 11 teams made of physicians from IOMC. The teams had at disposal 11 days to collect the data. Before collecting the data, the teams were instructed for two days, in a workshop.

The objectives of the training considered two components:

- theoretic, by understanding the requirements and responsibilities regarding the field activity, the ethic aspects regarding the women's approval for the participation in the study, the data protection;
- practical, by acquiring the knowledge and abilities necessary to the sampling, preservation and transport of the samples.

With the help of the study coordinators, the teams also established visitation schemes of the maternity clinics from the counties selected. The schemes were elaborated in such way that all the pregnant women hospitalized in the 7 days might be adopted in the study.

For the evaluation of the iodine status in the pregnant women, it was proceeded at the determination of the urinary iodine, with the ceric ammonium sulphate method. Such determination of the urinary iodine is based on spectrophotometric measurement of a complex colori metrabil at 420 nm; this complex is formed on the basis of the Sandel-Kholtoff reaction.

The average and frequency of the cases was considered, reported to the severity degrees, pursuant to the standards OMS/UNICEF/ICCIDD. The

normal values considered were those above 100 micrograms/l. The degrees of severity of the iodine deficiency are defined by the following values and intervals: <20 microg/l = severe deficiency, 20-49 micrograms/l = average deficiency, 50-99 micrograms/l = medium deficiency, >/= 100 microg/l = no deficiency.

For the evaluation of the iodine in the newborn the determination of the neo-natal TSH was used, obtained from a blood sample through the dry-spot method, in the first 5 days of life, made through the immunofluorescence method, the Delphia technique.

There were considered, pursuant to the standards OMS/UNICEF/ICCIDD, as deficiency, the TSH values in the newborn higher than 5 mUI/l, presented in a population larger than 3%.

The degrees of severity of the deficiency are given by the prevalence

- >/= 40,0% - severe deficiency;
- 20,0-39,9% - average deficiency;
- 3,0-19,9% - small deficiency;
- prevalence below 3% - no deficiency.

Results and discussions

The study results show an iodine deficiency within the limits of small deficiency in the pregnant women (50-99 microg/l) and average in the newborn, which accentuates the pathogenic risk. It was acknowledged that the prevalence of the congenital hypothyroidism is 1/4000-1/7000 newborn, having decreased from 2002 until 2008 and 2,8% from the newborn present transitory hypothyroidism.

The effect of the iodine deficiency on the newborn is materialized through a low weight at birth, the average of the weights at birth of such babies being lower than that of the general population. The thyroid pathology of the newborn is associated more frequently.

The neonatal TSH

The iodine level, the volume of the thyroid gland and the TSH are considered - by OMS, UNICEF, ICCIDD - indicators certifying the iodine deficiency in a population.

At population level, the level of the TSH is considered the best indicator in what regards the determination of the severity of the iodine deficiency in a population, as well as the risk of development of several affections related to iodine deficiency[1,2,3,4,5,6].

The adaptability of the TSH dosage to the method through the drop on filer paper has brought considerable benefits in the population studies regarding the iodine deficiency.

In the epidemiological studies, the limit value of normality for the neonatal TSH sampled from the integral blood is 5 mUI/l.

The evaluation of the iodine status is made function to the amount of the target population, with TSH values above 5 mUI/l. If higher values for more than 3% from the population are registered, it means that in the respective population there are iodine deficiencies. The severity degrees of the iodine deficiencies are delimited function to the amount of the population with TSH values above 5 mUI/l.

Thus, in the case of a prevalence between 3 and 19,9% the deficiency is low, at a prevalence between 20,0 and 39,9% the deficiency is average and when the amount of the population with TSH above 5 mUI/l is 40,0% the deficiency is considered severe (table 1).

It was evaluated the neo-natal TSH in a group of 969 babies of the mothers included in the study within this research component. The amount of those with values above 5 mUI/l was 31,3%, which encloses the iodine deficiency, according to OMS/UNICEF/ICCIDD, in the category of average deficiency (table 2, figure 1).

This doesn't point out any connection between the severity degree of the iodine deficiency of the mother (indicated through the level of iodine) and the iodine deficiency in the newborn (studied on the basis of the TSH median). Thus, for all the categories of severity of iodine deficiency of the mother there correspond values approximately equal of the TSH median in the newborn (table 3).

From the newborn tested, 2,8% had a TSH higher than 20 mUI/l, the standard value for suspicion of hypothyroidism (3,6% in the urban and 2,1% rural environment). These children are subject to some additional investigations in order to confirm the diagnosis (figure 2).

The median iodine level in pregnant women certifies a light deficiency,

Table 1

The degrees of severity of the iodine deficiency, by the amount of newborn with TSH values above 5 mUI/l

The degrees of severity of the iodine deficiency	The value ponderation for TSH in the blood >5mUI /L
Low level	3,0-19,9%
Average level	20,0–39,9%
High level	>/=40%

source: UNICEF, OMS, ICCIDD

Table 2

The distribution of the newborn by the limit value for the iodine deficiency of the TSH

Value for TSH (mUI /l)	Number of cases	%
<5 mUI/l (without deficit)	666	68,7
>5 mUI/l (with deficit)	303	31,3
Total	969	100

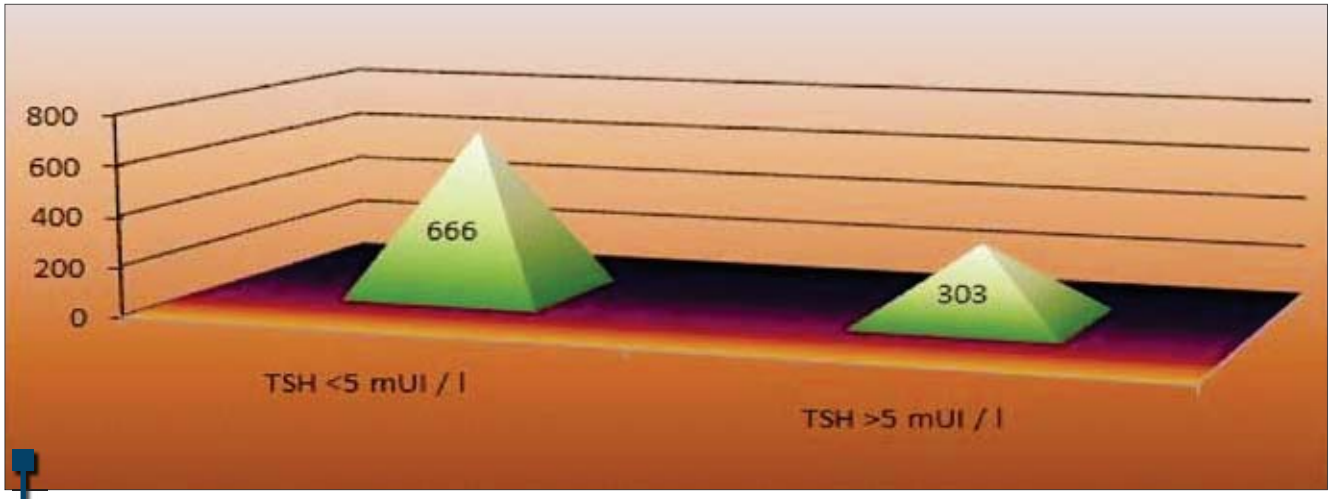

Figure 1. The distribution of the newborn by the standard value of the TSH for the iodine deficiency

while the percentage value of the newborn with TSH >5 mUI/l encloses the deficiency within the limits of average deficiency. Regarding this aspect, in the specialized literature it is appreciated that this phenomenon can be also explained with the fact that:

- The TSH is under the influence of some factors that can modify the dosage results, as well as the stress at birth and the utilization of some iodine antiseptic products;
- The utilization of the neo-natal TSH in the epidemiologic studies leads to a more severe enclosing of the iodine deficiency, compared to other methods, like the determination of the iodine level in school children or the palpation of the thyroid gland (Copeland and colab. 2002).

The weight at birth is one of the most important indicators of the health of the mother and of the child, both in developed countries and in the developing ones. In the specialized literature it is considered a factor of major importance in the establishment of the vital diagnosis and for the future development of the child.

Thus, the studies have shown that 50% from the neo-natal deaths occur in children with low weight at birth. A low weight at birth is considered a risk factor for subnutrition, recurrent infections and neuropsychic deficiencies[1,2,3,4].

The low weight at birth of the 1445 newborn in the study period was 2500

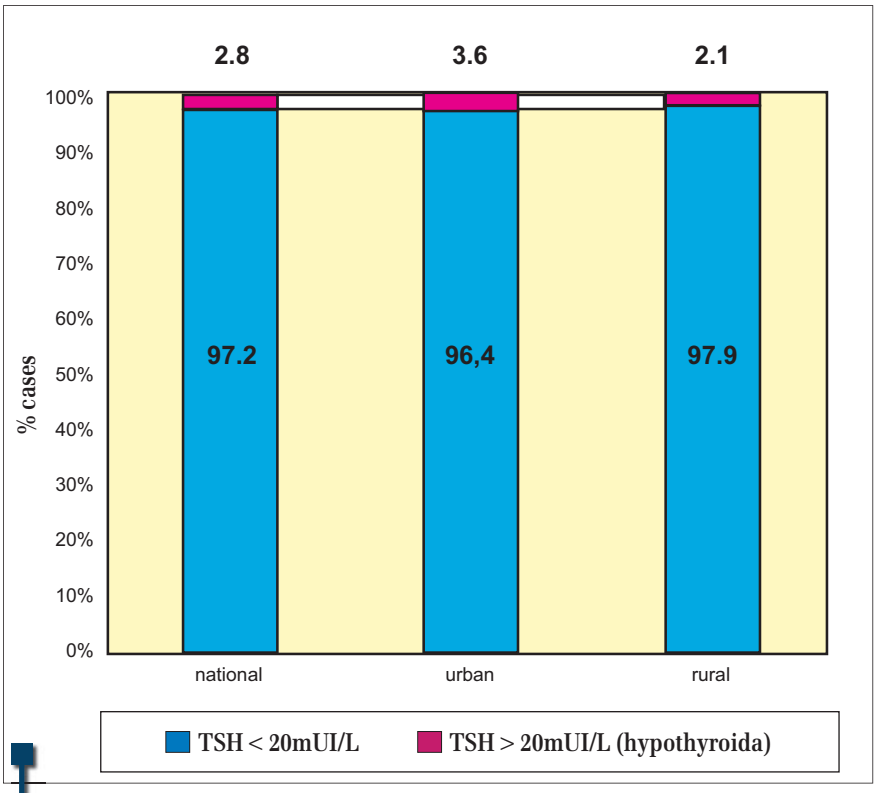

Figure 2. The distribution of newborns according to the standard TSH values for hypothyroidism, and the residence

grams, perfectly superposable on the one registered in the other components of the study, as well as in the previous studies from the specialized literature. We mention that the average of the weight at birth in the babies measured for the international reference standards is 3400 grams.

OMS defines as low weight at birth a weight lower than 2500 grams, regardless of the breeding age. The newborn with a weight at birth lower than the percentage 10 for their breeding age are considered babies with low weight for their age ("small for date")[3,4].

In this study, 6,9% from the children had low weight at birth, included premature born, and those with a lower weight than their breeding age (table 4).

Table 3

The average and the median of the child's TSH, function to the degree of iodine deficiency of the mother

The degree of iodine deficiency of the mother	TSH for the newborns (mUI/l)		
	The media	Standard deviatiation	The mediana
< 20 microgr/l	4,39	4,54	3,32
20-49 microgr/l	4,66	4,94	3,20
50-99 microgr/l	5,50	6,62	3,67
≥ 100 microgr/l	4,60	5,75	3,00

Table 4

The distribution of the newborn by the weight at birth, by average level of resistance

The weight at birth (gr)	Total		Urban		Rural	
	Number of cases	%	Number of cases	%	Number of cases	%
<2.500	99	6,9	44	6,3	55	7,4
2.500-2.999	337	23,3	151	21,6	186	24,9
3.000-3.499	578	40,0	282	40,3	296	39,7
3.500-4.000	363	25,1	191	27,4	172	23,1
>4.000	68	4,7	31	4,4	37	4,9
Total	1.445	100	699	100	746	100

Table 5

The distribution of the newborn by the weight at birth and the educational level of the mother

Weight at birth (gr)	Total	classes attended							
		< 5 classes		5-8 classes		9-12 classes		> 12 classes	
		N	%	N	%	N	%	N	%
<2.500	99	12	9,3	23	6,9	48	6,9	14	5,2
2.500-2.999	337	48	37,2	101	30,1	149	21,4	33	12,3
3.000-3.499	578	48	37,2	138	41,2	275	39,5	113	42,2
3.500-4.000	363	20	15,5	60	17,9	190	27,3	88	32,8
>4.000	68	1	0,8	13	3,9	34	4,9	20	7,5
Total number of cases	1.445	129	100	335	100	696	100	268	100

A low weight at birth is more frequent in the rural environment, which inscribes in the general development characteristics, more precarious in the rural than in the urban environment. The prevalence of a low weight at birth is higher in the children coming from mothers with low school level (below 5 classes), being almost double compared to the children coming from mothers with over 12 classes (table 5).

The social-economic level of the mothers differentiated less the prevalence of the low weight at birth than the school level (figure nr. 3).

The results of this study confirm the data from the specialized literature.

The research published in the Romanian literature regarding the suspicion of hypothyroidism pointed out that the frequency of neonatal deficiency is higher in the urban environment (3,6%) than in the rural (2,1%)[4].

The problem is that the congenital hypothyroidism is not clinically obvious at birth. Fortunately, children with congenial hypothyroidism have low T4 and high TSH, concentrations that can be easily noticed in the blood, and the treatment administered before the age of 3 months is usually followed by a normal development[5,7].

Van Tijn and colab. have made a multicentric study for the diagnosis of the newborn with congenital hypothyroidism considering in this purpose TBG, T4 and TSH. A central congenital hypothyroidism was diagnosed when the T4 concentration was lower than 1.6 DS, if the report T4/TBG was lower than 8.5 and if the TSH was lower than 20 mU/l.

Recent research (Passalidou I. si colab.), through successive dosages of TSH, T3, T4 - blood samples from the newborn heel bone have pointed out anatomic anomalies of the gland (90%), while other cases include a therapeutic administration of radioactive iodine and other anti-thyroidal that can affect the thyroid function and can lead to the debut of the disease in the postnatal period[8].

The level of thyroid hormones differ function to the prematurity degree (23-36 weeks of pregnancy); thus, the values of the thyroid hormones sampled from the umbilical chord of the premature babies and from the postnatal serum differ from those of the newborn born at term or of the adults.

Longitudinal studies made within groups with growing intrauterine restriction regarding the pregnancy age vary function to the average and the nature of the parameters analysed. The reference field of the thyroid hormones in prematures derives from the plasmatic levels sampled during the first weeks of life. First of all, the answer of the hypothalamic - pituitary-thyroid axis is reduced in the premature newborn at birth for an undetermined postnatal period. On the other hand, there are studies that showed the newborn with a very low weight at birth have low serum concentrations T3 and T4[9,10].

This is accompanied, in the fetuses with IUGR, by a reduction of the expression of all the forms of receptors for thyroid hormones at the level of the cerebellum and of the cortical substance, pursuant to the studies of Verhaeg and colab[10,11].

Pursuant to the research of Van Wassenaer's team, the premature newborn with breeding age lower than 30 we-

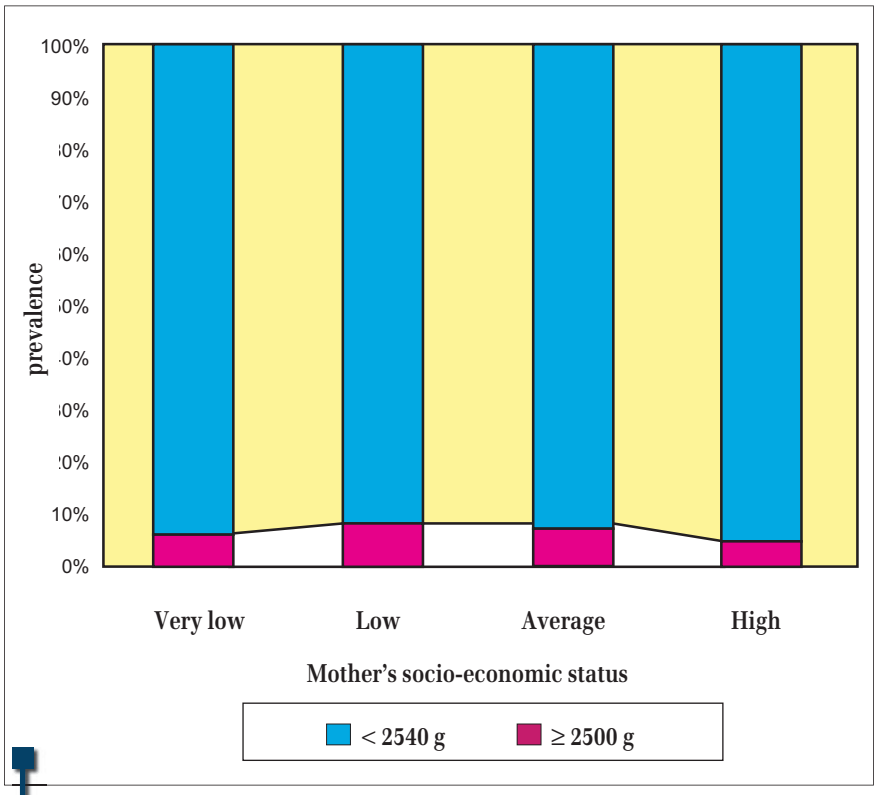

Figure 3. The distribution of the newborn by the weight at birth and the social-economic level of the mothers

eks (not necessarily with IUGR) can present a period of hypothyroxinemy with a serum breakdown of the free fraction T4, without an increase in the TSH. These newborn present problem with the self-adjustment of the iodine at the level of the thyroid, as well as an immaturity of the hypothalamic - pituitary-thyroid axis, which leads to the inability of compensating the loss of maternal T4 in a short time[12].

Ares and colab. have compared the concentrations of the free fractions of T4 of the premature newborn with those of the fetuses in utero with the same breeding age, and they have noticed a decrease by 50% in the first case, a phenomenon not noticed in the newborn at term[13].

The TSH, the iodine level and the volume of the thyroid gland are considered, by OMS, indicators certifying the iodine deficiency in a population. The studies have pointed out that at population level, the TSH value on the newborn is considered the best indicator in what regards the determination of the severity of the iodine deficiency, as well as the risk of development of certain affections based on iodine deficiency. Thus, pursuant to the studies of Delange, as well those of other authors, the limit value established to define a normal level for the TSH sampled from the integral blood is 5 mU/l[17-22].

Within the neonatal screening, the sampling for the TSH dosage refers to the blood sampled on filter paper. In this case, the values expressed by the specialized literature and pursuant to the protocols of OMS are standardized for the days 3-5 postnatal, and the interpretation of the values obtained cannot be made, since in the specialized literature consulted they are not standardized. If we report only to the neonatal TSH, the immediate sampling after birth seems not to be a relevant indicator of the iodine deficiency. According to some authors, this would be due to the iodine deficiency which reduces the TSH peak. Other studies have shown that the TSH peak lowers as the prematurity degree rises [23,24,25].

Generally, the evaluation of the iodine deficiency is made function to the amount of the target population with TSH values much higher than 5 mU/l. Thus, if for more than 3% from a population TSH values above 5 mU/l are registered, it means that in the respective population there is iodine deficiency. The appreciation of the iodine deficiency severity is made function to the amount of the TSH values above 5 mU/l, within the sample of the population studied.

A prevalence contained between 3-19,9% certifies a low deficiency, a prevalence contained between 20-39,9% an average deficiency and above 40,0%, the iodine deficiency is considered severe. If before the application of the universal law of iodine level in the salt the studies made in our country showed a discrepancy between the severity of the iodine deficiency in the pregnant woman and that of the newborn, now the situation has changed, and both the mother and the child can be found within the same class of iodine deficiency - low.

Thus, in the pregnant women the low deficiency is pointed out by the level of iodine (71.73 ± 26.54 µg/L); in the newborn the appreciation of the low deficiency is pointed out by the amount of the serum TSH value above 10 mU/I (5.73 ± 3.1 mU/1). This iodine deficiency can be evaluated correctly immediately after birth only through a combined utilization of other parameters as well (such as iodine level and the volume of the thyroid gland).

This is necessary because the level of neonatal TSH depends on a series of factors that can affect the dosage results (from the most important we can mention the stress before birth and the sue of iodine-based antiseptic products)[26].

In what regards the connection between the stress and the TSH level, certain studies have shown a connection with the stress determined by the labour. In what regards the moment of occurrence of the TSH peak and its amplitude in relation with the birth stress, pursuant to the data from the literature, it varies with the prematurity degree, registering values of approx. 8 mU/I in premature.

Another reason of caution in the interpretation of the neonatal TSH values includes the sensitivity of the dosage method used (for example, ra-

dio- or fluor-imuno-dosage) determines minor differences regarding the results obtained, but enough to influence the proportion of the results above the preset values of the cut-off (of 3 mUI/L by certain authors). The dosage method of TSH - META, a third generation kit, practically increases its sensitivity.

Conclusions

The complexity of the etiology and of the consequences of the thyroid hormone deficiency recommends the necessity of interdisciplinary and intersectorial collaboration in the rapid discovery of the affection and the initiation of an adequate care both in the case of the pregnant and of the newborn.

The appreciation of the iodine deficiency through the determination of neo-natal TSH encloses the population studied in the average deficiency category. There occurs a discrepancy between the severity of the iodine deficiency in the pregnant, evaluated through the iodine level median, and the iodine deficiency in the newborn, evaluated through the percentage report of the cases with neo-natal TSH higher than 5 mUI/l. In the specialized literature certain studies consider the values of the neo-natal TSH as the most appropriate indicator of the iodine deficiency at the level of the population.

It is particularly useful the inclusion in the prenatal consultation the determination of the iodine deficiency, as a possible cause of insufficiency of thyroid hormones, the prophylaxis of such deficiency, and postnatal, the determination through screening of the congenital hypothyroidism. The susceptibility of the fetal brain, in course of development, to lesions caused by lack of iodine imposes an effort of evaluation and monitoring of the iodine deficiency in the pregnant woman and in the baby. The iodine deficiency must be monitored as well after the implementation of a control strategy for such deficiency.

It is important that physicians of various specializations (gynecologists, general medicine specialists, specialists in public health, endocrinologists), public health educators and other categories of staff coming in contact with the pregnant woman (average medical staff, psychologists) work together in the control of the iodine deficiency.

The screening programs for congenital hypothyroidism are "matured" and at present they are operational at world level. They are certainly extremely beneficial and efficient, eliminating the major neuropsychic problems that always occur in the children with untreated congenital hypothyroidism. ■

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