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# Hypothyroxinemia in Pregnancy is Related with Attention Deficit Hyperactivity Disorder

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## 1. Introduction

As previously published material has demonstrated, there is a prevalence of 70% of ADHD in children with thyroid hormone syndrome (GRTH)<sup>1</sup>, a disorder caused by a mutation in the gene of the thyroid receptor B and characterized by a lowered response to the action of thyroid hormones at pituitary and peripheral tissue levels. Vermiglio<sup>2</sup> have conducted a study that relates the maternal hypothyroxinemia in different trimesters of pregnancy for the development of the child, followed by up to 10 years age. The most important finding, and totally unexpected, was that 70% of the offspring of mothers, with mild iododeficiency had ADHD, while it is not diagnosed in offspring of mothers in a control area without iodo insufficiency. The similarity of the results of these studies would appear to point out that there could be a potential relationship between the neurophysiologic disorder, the GRTH syndrome and the impaired thyroid hormone action. This could be either because of low levels of maternal thyroxine which are due to an insufficient previous iodine intake before and during pregnancy or a defect in the thyroid hormone receptor.

When iodine deficiency is present during the earlier stages of pregnancy and early brain development, leads to neurological cretinism. Throughout gestation, the maternal thyroxine (T4) is transferred to the fetus through the placenta and has a neuroprotective role. The free T4 in the fetal fluids increases in parallel to the maternal T4, and therefore a normal maternal thyroxinemia is of utmost importance for the protection of the fetal brain.

In this chapter we discuss the thyroid hormones and their influence during fetal brain development, by studying the changes covered by these hormones during fetal development and the influence of maternal thyroid function for proper fetal brain development

Thyroid hormones (TH) are secreted mostly as thyroxine (T4) from the thyroid gland and transformed in diverse tissues to the transcriptionally active form 3,5,3' -triiodothyronine (T3) to the deiodinases type 1 and 2 (D1,D2) (Yen,2001). T3 plays a key role during the central nervous' system (CNS) development. During development, T3 is needed for the normal expression of genes which are critically involved in many processes, especially in neuronal migration and differentiation. Deficiency during the fetal and early postnatal period leads to striking abnormalities in dendritic an axonal growth, synaptogenesis,

neuronal migration, myelination and also neuronal cell death (Chan and Kilby, 2000). T4 treatment immediately after birth is enough to prevent most of the brain damage induced by neonatal hypothyroidism. Such treatment, however, cannot fully rescue abnormal brain development, induced by hypothyroidism in the uterus (i.e., by maternal iodine deficiency) (Koibuchi and Iwasaki, 2006).

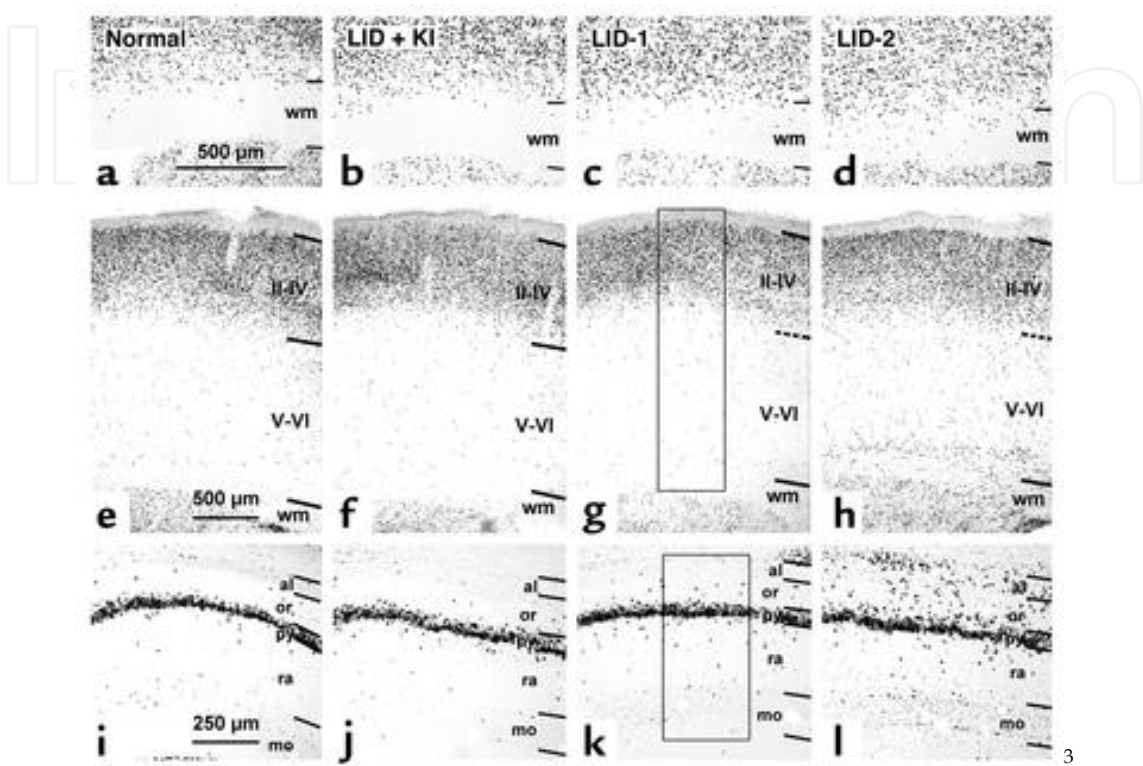


Fig. 1. Cortical cell migration in rats induced by a low iodine diet

T3 regulates TRH expression in developing hypothalamic neurons in vitro. The supply, needs a proper concentration of T3 for a normal neuronal development. The data that A. Carreón-Rodriguez et al 2009 presented suggested that T3 plays a key role not only in the HPT axis function but also in its development. Its mechanism is unknown; therefore, an adequate balance of time and concentration of TR isoforms may determine the set point for TRH expression to consequently regulate thyroid hormone levels. An imbalance during the development of the neuroendocrine TR isoforms could result in neurological diseases (ADHD, obesity, anorexia nervosa, subclinical hypothyroidism, etc. (Siesser et al., 2005, 2006; Reinehr et al, 2008)

1.1 Pregnancy and thyroid function

Hormonal and metabolic changes during pregnancy result in profound alterations of the biochemical parameters of the thyroid function (D Glioner 2001). In regard to this, the main event that can occur during pregnancy is a marked increase in serum thyroxin-binding globulin levels. This change will require an increased hormonal output by the maternal thyroid gland. The metabolic adjustment will be unable to be reached when the functional capacity of the thyroid gland is impaired because of iodine deficiency or (TAI) thyroid autoimmunity

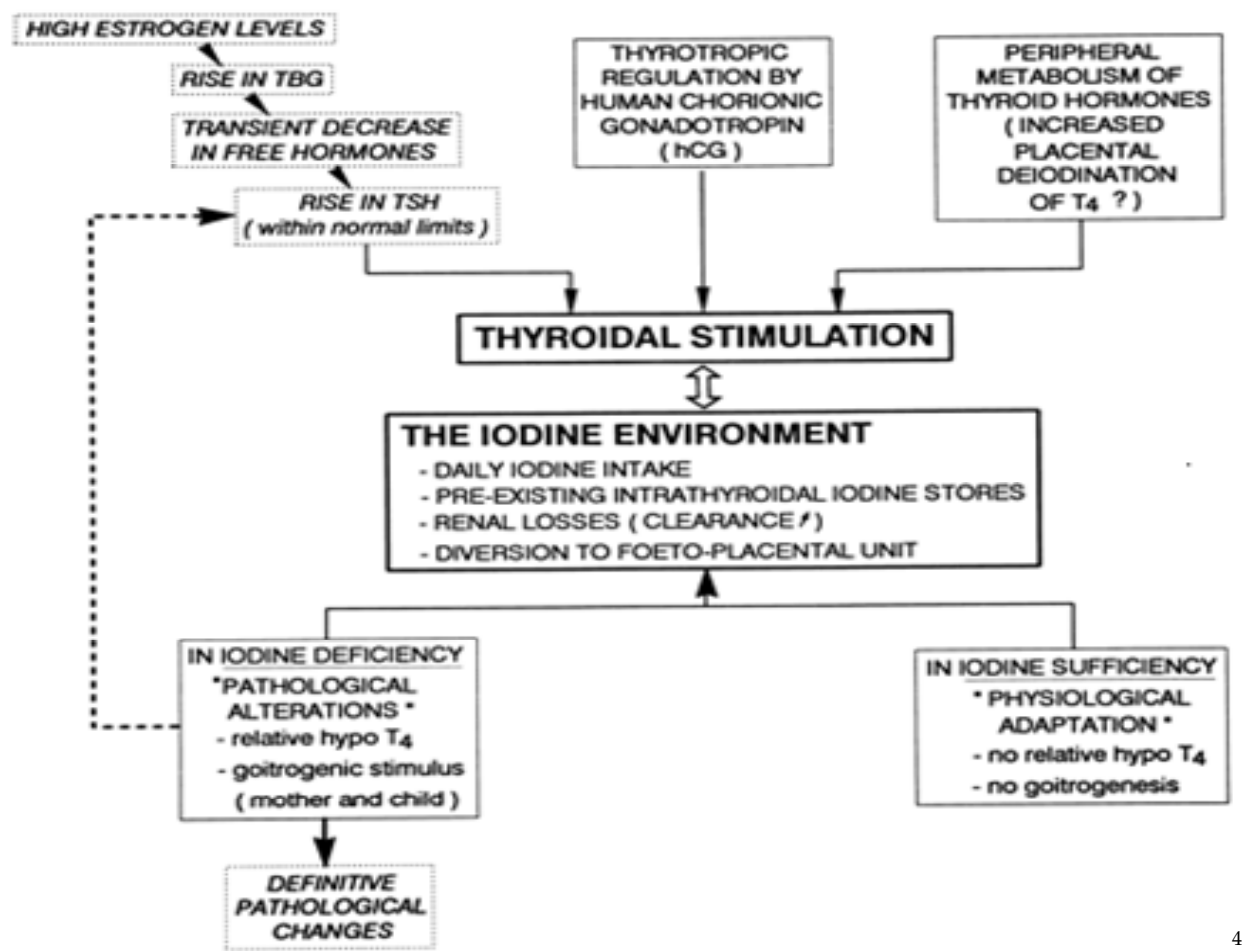


Fig. 2.

1.2 Fetal thyroid physiology

Fetal thyroid function starts to occur at the end of the first trimester. Before that, there is evidence that the normal development of the fetal brain is dependent upon maternally derived T4, which is converted intracellularly to T3. This T4 starts to be detected from the 5 to 8 gestation week and by the time pregnancy reaches 11 weeks it is 100 times more concentrated than in the maternal circulation. Maternal hypothyroxinaemia at this stage may have adverse effects on subsequent fetal brain development (J C Girling 2006)

Fetal fT4 and total T4 reach adult levels by 36 weeks' gestation, fetal TSH is greater than adult TSH and fetal T3 remains low. The relatively high levels of T4 allow intracellular conversion to T3 in the fetal brain. So the maternally derived T4 becomes essential to allow normal neurological development. Placental perfusion studies have demonstrated that, in a normal pregnancy very little (0.008%) maternal T4 crosses to the fetal side; inhibition of placental diiodination of T4 enhances transfer 2700-fold so that fetal levels reach 30% of maternal concentrations. In a pregnancy complicated by fetal thyroid dysfunction deiodinase III is inhibited, allowing additional transfer of t4 to the fetus reducing fetal peripheral deiodination of t4 and enhancing intracellular activation of T3 in the fetal brain, protecting it from permanent damage.

### 1.3 Iodine deficiency

Iodine deficiency results in cretinism in newborns, goiter in adults and reduced reproductive success in women. More than one billion people worldwide are affected by iodine deficiency and more than 20 million people have adverse neurological sequelae that followed fetal iodine deprivation. Neurological endemic cretinism is the leading preventable cause of mental retardation and has a major negative effect on the economy of afflicted areas. In iodine-deficient populations, 2-10% of individuals are affected; in these populations, a mild degree of mental retardation is five times more common than cretinism itself, resulting in a left shift of the intelligence quotient (IQ) distribution curve by 10 points. Cretinism is characterized by deaf mutism, intellectual deficiency, spastic motor disorder and, in some cases, hypothyroidism.

### 1.4 Thyroid autoimmunity

There is increasing evidence that mainly nutritive factors and environmental pollution by metals and chemicals (organ chlorines, pesticides) are the main factors in the present-day spread of this disease. TAI (thyroid autoimmunity) nowadays affects at least the 10% of the population of North America and Europe<sup>5</sup>

It can therefore be assumed that the role of genetic and environmental factors is of utmost importance for the triggering of the disease, with the susceptibility genes contributing by an 80% and environmental factors by a 20% (Tomer Y et al 2009)

The link between nutrigenomics, proteomics and metabolomics is likely to provide a platform for prevention and enhanced treatment of TAI.

It has been reported that certain epigenetic factors are dependent on specific food components such as metals and pollutants increase an individual's susceptibility to type 1 diabetes mellitus or Crohn's disease. These findings unmask a pathogenetic association<sup>6</sup>

It is thus apparent that the environment may play a decisive role in modifying genetic expression via epigenetic mechanism by triggering autoimmunity<sup>7</sup>

### 1.5 Pollutants

Recently, a study in Brazil assessing the prevalence of HT and thyroid antibodies in residents of an area surrounding a petrochemical complex reported a higher incidence of HT (9,3% and anti-thyroid antibodies than in the center area of Sao Paulo)<sup>8</sup>

There is also increasing concern regarding a possible linkage between chronic exposure to both solvents (benzene) and air pollutants (carbon monoxide) with thyroid and respiratory functioning. A recent study that investigated the long-term effects of the exposure to benzene and carbon monoxide in a group of non-smoking petrol station attendants marked increase in T4 and fT4 and decrease in TSH and T3 serum levels<sup>9</sup>

A hypothesis to this was that the organochlorines (OC) body burdens in the young adults were in fact a consequence to the exposure to high levels of OC by their mothers, during the offspring's prenatal and perinatal life<sup>10</sup>



Another study undertaken in East Slovakia showed that fish from waters in the surrounding region consumed by the local population were becoming the prime source of ingested PCBs and pesticides, this leading to a rising incidence of goiter and autoimmunity<sup>11</sup>.

What causes this to happen still remains unclear. However, in an experimental study that researched the thyroid function in Sprague-Dawley rats after exposure to Aroclor (PCB s group), distinct histopathological changes such as hyperplasia of epithelia in follicles, reduction of colloid content and lymphocytic infiltration into the perifollicular areas, were observed<sup>12</sup>. In parallel, the decreased FT3 and FT4 and the increased TSH serum concentrations and TPOAB titers indicated that PCBs affect thyroid functioning by inducing autoimmunity.

### 1.6 Smoking

Tobacco smoke contains several potent goitrogens, which interfere with the NIS (cotransportador NA/I<sup>+</sup>), TPO and dual oxidase (DUOX) activities, rendering smoking a major risk factor for thyroid disease.

Smoking may cause the development of thyroid-associated ophthalmopathy in patients with Grave's disease. Smokers receiving radioiodine have the highest incidence of deterioration or recurrence of this disorder<sup>13</sup>

Second-hand smoke (SHS) exposure disrupts thyroid function and induces inflammatory stress by increasing IL-1 $\beta$  which impairs thyroid hormone synthesis and iodine uptake<sup>14</sup>.

It is evident that, as SHS exposure disrupts human biological systems via thyroid impairment, preventive and educational measures should urgently be undertaken to protect against SHS via radical reduction of smoking.

### 1.7 Fetal programming of infant neuromotor development

Neuromotor impairment can be caused by damage to the immature brain during delivery or by medical interventions performed after birth. However, it is more likely that deviances in the brain development originate before birth. A theory that relies on this early origin is the "Fetal Programming Hypothesis"<sup>15</sup> which states that fetuses adapt to limited supplies of nutrition and oxygen. These adaptations program the fetus physiology, metabolism and growth, increasing the risk of later diseases: cardiovascular and mental problems<sup>16</sup>

Clinical deteriorations are determined primarily by the gestational age of disease onset and placental blood flow resistance<sup>17</sup>. Fetal acidemia carries a greater risk of irreversible developmental delay<sup>18</sup>, rather than hypoxemia. Delivery timing and compromise degree at birth can modify infant neurodevelopment (GRIT- Growth Restriction Intervention Trial). The proportion of essential substrates that are metabolized aerobically in the liver and their ability to drive the endocrine growth axis of the fetus is influenced by the degree of placental dysfunction. When nutritional deficiency is severe enough or has persisted for a considerable long period of time, the growth rate of all fetal measurements slows down and the sonographically estimated fetal weight eventually drops below the 10<sup>th</sup> percentile<sup>19</sup>

The metabolic status and the diminishing supply of glucose force the brain and heart to metabolize lactate and ketones as their primary energy sources<sup>20</sup>. With increasing severity of placental dysfunction the transfer of these important nutrients also becomes impaired and their deficiency is linked independently to a range of neurodevelopmental disorders<sup>21</sup>. The rate of deterioration of cardiovascular parameters determines the overall speed of deterioration in early-onset FGR (Fetal Growth Restriction), often needing preterm delivery. According to this, fetuses are forced to make critical adjustments in their cerebral metabolism of essential nutrients prior to delivery. Although term FGR (Fetal Growth Restricted) does not present the same degree of clinical deterioration as early-onset disease does, abnormal brain microstructure and metabolism have been documented independently of the degree of vascular Doppler abnormalities, probably reflecting the increasing sophistication of central nervous system with accelerating synapse formation.

In summary, there is evidence that placental dysfunction is associated with delayed achievement of behavioral state organization prior to deterioration of fetal status. A recent study documented suboptimal scores for social-interactive, attention capacity, state organization and motor skills among growth-restricted neonates that had abnormal prenatal MCA (mean cerebral artery) Doppler studies<sup>22</sup>

To avoid bias, as to the cause of neurological impairment, in our study, we have discarded all newborns below the 10<sup>th</sup> percentile of weight.

In our previous study, logistic regression analysis showed that the offspring of mothers with gestational hypothyroxinemia had an adjusted odds ratio of 3.9 (IC 95%, 1.1-14.2  $p=0.036$ ) of having an abnormal ADHD test score. But it could be argued that the age of the studied children was under the recommended age for making a diagnosis. Today, four years later, we included the 58 pregnant women of the previous study, plus 12 selected mothers who present lower values of T4 in order to increase the difference between the two study groups.

## 2. Aim

The aim of the present study is to compare the scores obtained from testing for ADHD in children whose mothers had low T4 ( $< 0.79$ ) values in third trimester of pregnancy.

## 3. Methods

ADHD test was applied to the mothers by a trained interviewer and the answers obtained from the set of questions, were expressed as a score according to the detection of the different symptoms of ADHD. The test included the three different dimensions of the syndrome: attention, hyperactivity and impulsivity, with a total of 18 items. The diagnosis of ADHD according to DSM IV requires the existence of 6 symptoms of inattention and 6 symptoms of hyperactivity-impulsivity; although the positive diagnosis of ADHD requires a more complex psychological evaluation together with additional information obtained from the parents and school teachers during a six month period, a test a high score of which is highly suspicious of ADHD.

### 3.1 Population sample

Pregnant women who were attended during 2003-2004 in the Hospital Clinic of Barcelona, a tertiary referral hospital which covers a geographical area of mild iodine deficiency<sup>23</sup> participated in the study and were evaluated for thyroid function in the third trimester of gestation. Those who had history of thyroid problems as they had already received antithyroid and/or thyroid hormonal treatment were excluded of this study. The first study group was formed by only those who presented FT4 values less than 0,79 ng/dl, which is the percentile 10 of the distribution of T4 in pregnant women in our area in the third trimester of pregnancy<sup>24</sup>. The final study group accomplishing the aforementioned criteria was composed by 40 women. The control group (n= 31) was selected in a randomized fashion by means of the SPSS program among 442 women of an original cohort who had normal FT4 values. Eventually a total of 69 women and 71 children were analyzed.

Each mother gave her consent for participation in the study and permission was obtained from the Ethics Committee of the Hospital.

### 3.2 Measurements

FT4 was measured by using an immunoassay (ADVIA-Centaur, Bayer) with a CV of 5.4%.

In order to evaluate the syndrome, a test from the 4<sup>th</sup> edition of the revised manual for the diagnostic and gravity of mental illnesses was used<sup>25</sup>. The ADHD test was administered to the mothers by a trained interviewer which did not know if the participant was included in the study or control group.

## 4. Results

No significant differences were observed between the study group and the control group in relation to maternal age, gestational age at the time of delivery, birth weight, sex of child and Apgar scores at one and five minutes:

Children whose mothers had low levels of FT4 showed a significantly higher average score in the total score of ADHD test; also, they had higher scores in the scales of inattention and impulsivity when evaluated separately.

Unlike the previous study, the hyperactivity scale, when evaluated independently, is not significant; which is consistent with the clinic, because as the child gets older the symptoms of hyperactivity decrease.

In the study group, three children were diagnosed and on treatment. One of those kids has mental retardation and laxity in the hands. The other child has serious family problems. Eight children showed high test score. Of these, one is stuttering and two have hearing loss. Two more children were being studied under suspicion of having the syndrome by a professional.

Within the control group a child was diagnosed with attention deficit disorder, and in the other child, the syndrome was ruled out after psychological evaluation.



	FT4<0,79 ng/ dl N=40	FT4≥0,79 ng/ dl N=31	p
Maternal age (mean)	32,6	31,4	0,256
Weeks delivery (mean)	39,05	39,8	0,032
Birth date (mean)	13.03.2004	27.08.2004	0,018
Birth weight (mean)	3310	3488	0,122
Sex newborn (mean)	1,58	1,42	0,199
Apgar 1' (mean)	8,90	8,84	0,677
Apgar 5' (mean)	9,95	9,87	0,535

Table 1. Characteristics of the study groups

	FT4<0,79 ng/ dl N=40	FT4≥0,79 ng/ dl N=31	95%Confidence Interval for mean	p
Inattention score; (mean; SD)	20,55; 8,74	13,5 ; 6,14	15,5-19,5	0,000
Hyperactivity score (mean; SD)	14,33; 5,45	10,87; 5,37	11,4-14,2	0,010
Impulsivity score (mean; SD)	10,48; 4,18	5,97; 2,78	7,5 - 9,5	0,000
Total score (mean; SD)	45,35;16,04	30,39; 12,05	42,6-17	0,000

SD: Standard Deviation

Table 2. Score of ADHD test

## 5. Discussion

The ADHD is a neurobiological disorder with a multifactorial origin, where heritability is of 0, 8 and is of polygenic character. There are several environmental factors that could increase its frequency in which hypothyroxinaemia during pregnancy may play a role. In our study, we found an association between low maternal thyroxine levels at third trimester and a high ADHA score in the children of those mothers.

In humans, the relationship between maternal nutrition and the incidence of neural-tube defects has been actively explored. Smithells et al<sup>26</sup> conducted a controlled study of supplementation with multivitamins, including folic acid, to test their effect on prevention of neural-tube defects. The results demonstrated that women who received multivitamin supplementation before conception and during the first 2 months of pregnancy had significantly reduced the risk of neural-tube defects compared to unsupplemented women.

The revision of the data above, lead to the conclusion that the effect of iodine deficiency on the human fetal brain, occurred during the second (and probably) third trimester. The duration of hypothyroidism during development may crucially affect neurological disability.

One of the most important experiments of nature in regard to brain development is the neuropathological picture in endemic cretinism, in which maternal hypothyroxinemia and fetal hypothyroidism, both induced by iodine deficiency, combine during a critical period of fetal development, produce a critical degree of thyroxine deficiency severe and prolonged enough to cause irreversible damage to the ongoing program of neural development.

Fortunately, the application of different iodization programs has paid off. But both environmental pollution and depletion of croplands make that moderate iododeficiency persists in some areas of the planet. It also increases autoimmune thyroid diseases, which can cause hypothyroxinemia in situations of high demand such as pregnancy.

On the other hand, a recent survey estimates an increase of about 22% in ADHD from 2003 to the most recent survey in 2007-08. This data was obtained by the Centre for Disease Control and Prevention (CDC) that interviewed parents who had children between the ages of 4 and 17.

Researchers calculate that 5.4 million kids have been diagnosed with ADHD, which suggests that the amount of children with this disease has increased by 1 million in the last few years. Scientists don't have a clear answer about why there has been such a significant increase. Study lead author Susanna Visser of the CDC, suggests that a greater awareness of the problem in society and stepped-up screening efforts is part of the explanation.

We can no longer run the risk of letting any more children - including those with ADHD - fail at school. Their failure reflects in not only the recent increase in "dropping-out" unemployment but also reflects in a major claim of welfare benefits, more problems with authority and penal incarceration. It also privates society of the contribution these individuals could have made if their potential been developed.

In 1999 Pop<sup>27</sup> found significant physical and psychomotor abnormalities in children who had mothers with hypothyroidism at 12 weeks of gestational age, where as at 32 weeks no differences were found, and this is possibly due to the fact that between 16-20 weeks, the foetus begins to synthesize its own thyroid hormones and mothers with a defective thyroid function in week 32, were having an acceptable thyroxine production during the first trimester.

In our study we only have T4 values of the third trimester, However, performing a prospective study that followed up to ten years or more hipotiroxinemic mothers, could be a very interesting way to answer definitely the question if low t4 values are related with the presence of ADHD in the progeny of those mothers.

The best assessment in order to avoid this chronic disease that would need treatment for life is prevention. Measures can include: Reduction of intrauterine pollution, appropriate supplementation of the pregnant mother with vitamins and a universal screening of thyroid function in pregnant women within their reproductive age, for the correction of gestational hypothyroxinemia at the right time of pregnancy.

This will be the only way to decrease the portion of ADHD related to hipotiroxinemia.

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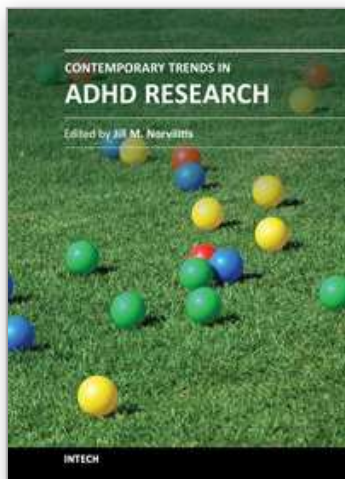
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## **Contemporary Trends in ADHD Research**

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With many children and adults affected by Attention Deficit Hyperactivity Disorder, researchers strive to understand the underpinnings of ADHD and associated factors on both a basic and applied level. The goal of this volume is to explore some of the broad array of research in the field of ADHD. The 12 chapters cover a variety of topics as varied as postural control, endocrine dysfunction, juvenile justice, and academic outcomes. These chapters will provide valuable insights for students reading about ADHD for the first time, researchers wishing to learn about the latest advances, and practitioners seeking new insight in the field.

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