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CLINICAL STUDIES

Normal intellectual development in children born from women with hypothyroxinemia during their pregnancy

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ABSTRACT

Proper maternal thyroid function is known to be essential for neural differentiation and migration in the fetus during the first half of pregnancy. The objectives of this study were to assess the relationship between thyroxin levels, in pregnant women with no thyroid disease and the intellectual development of their offspring in a non-iodine-deficient area, and to know specifically whether or not isolated hypothyroxinemia during pregnancy was associated with a lower intelligence in the offspring.

Previously we had publicated values TSH, FT4, free T3 (FT3), anti-thyroid peroxidase antibodies (TPO Abs) and urinary iodine concentration (UIC) in 1322 pregnant women in our hospital area. Now we presented results of intelligence quotient in children born from these pregnancies. We assessed 455 children at one year of age using Brunet-Lezine scale. Of these, 289 children were evaluated again at 6–8 years of age using the WISC-IV. From the total group of children recruited, we established as control subgroup, children born of rigorously normal pregnancies (women with UIC > 150 μg/L, FT4 > 10th percentile and TPO-Ab negative in both trimesters). The remaining children were divided into two subgroups: those born to mothers with FT4 below the 10th percentile and the rest. No correlation was found between FT4 maternal levels, in either of trimesters studied, and the intellectual scores of offspring. No differences were found in intellectual scores comparing children born to mothers with hypothyroxinemia and those whose mothers were euthyroxinemic in both trimesters, or with the control subgroup.

As conclusions we did not find any association between the levels of maternal FT4 during pregnancy and the subsequent intellectual development the offspring from these pregnancies. We attribute this result to the fact that all the pregnant women included had normal thyroid function.

Introduction

The thyroid hormones, triiodothyronine (T3) and tetraiodothyronine (T4) play an essential role in cell metabolism and in the growth and development of body organs. The fetal period and early childhood are critical times for human brain development. It has been confirmed that the fetal thyroid gland is not able to synthetize thyroid hormones until 14–16 weeks of pregnancy; therefore, for neural differentiation and migration in the fetus, proper maternal thyroid function is essential in the first half of pregnancy. During this period, as T3, the active form of the thyroid hormone, does not cross the fetal blood–brain barrier, the fetal brain is dependent on maternal T4 and its local conversion to T3 [1–6]. Given

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Table 1
Urinary iodine concentration (UIC) and thyroid function in pregnant women.

	Total pregnant women (Ref. [9]) *N* 1322		Pregnant women included *N* 512	
	T1	T2	T1	T2
Median UIC (μg/L)	88.5	140	75.5	134
Mean FT4 ± SD (pmol/L)	17.26 ± 3.1	14.32 ± 1.9	16.73 ± 2.31	14.15 ± 1.93
Mean FT3 ± SD (pmol/L)	6.0 ± 1.3	6.23 ± 1.3	5.95 ± 1.18	6.18 ± 1.22
Mean TSH ± SD (mU/L)	1.78 ± 8.9	2.06 ± 3.5	1.44 ± 1.28	2.0 ± 1.8

T1: first trimester and T2: second trimester.

that iodine is essential for the synthesis of thyroid hormones, children born in severely iodine-deficient areas are at greater risk of irreversible brain damage and mental retardation due to the effects of maternal and fetal hypothyroxinemia during pregnancy [7,8]. However, there is still no consensus on the effect of isolated maternal hypothyroxinemia on the intellectual development of offspring. In an attempt to clarify this issue, we decided to explore the relationship between the thyroid levels in pregnant women with no thyroid disease and the intellectual development of the children born from these pregnancies, and specifically to assess whether isolated hypothyroxinemia (free T4 (FT4) < 10th percentile) during pregnancy is associated with lower intelligence in the offspring.

Materials and methods

Previous study by the authors

Between April 2002 and October 2004, a total of 1322 pregnant women in the catchment area of hospital were included in a study to analyze autoimmunity and thyroid function. Serum TSH, FT4, free T3 (FT3), anti-thyroid peroxidase antibodies (TPO-Abs) and urinary iodine concentration (UIC) were measured during their routine obstetric visits at the end of the first trimester (T1) and at the end of the second trimester (T2). Women were excluded if they had any serious health problem as well as if they had TSH > 5 μU/ml or TSH < 0.01 μU/ml with FT4 > 25.7 pmol/L. The detailed study protocol and test results during pregnancy have been reported previously [9] and are shown in Table 1.

The study was conducted in an area with adequate UIC levels in school-aged and adolescent populations [10,11]. We considered hypothyroxinemia those FT4 values below the 10th percentile (13.7 pmol/L in T1 and 11.5 pmol/L in T2).

Study subjects

We designed a prospective observational double-blind study to analyze intellectual development in children born to the aforementioned cohort of pregnant women. Participating women were contacted randomly at the end of the first year of life of their children. Parental informed oral consent was obtained to assess the children using the Brunet-Lezine (BL) scale. Supplementary information about the child's health status was also systematically requested at the time of the visit. Multiple gestations, preterm infants, small newborn for gestational age and children with congenital anomalies were excluded. In addition, four children were excluded due to serious health problems during their first year of life. When children reached an age between 6 and 8 years, we assessed their intellectual ability with the Wechsler Intelligence Scale for Children (WISC-IV) at dedicated appointments, arranged by random telephone calls. For this assessment, we obtained written informed consent from all the parents who agreed to participate. At this stage, we excluded four children who had been diagnosed with a pervasive developmental disorder (Table 2). No socioeconomic data were collected.

All intellectual assessments were performed by the same two psychologists. The study protocol was approved by the Clinical Research Ethics Committee of Hospital Universitario Cruces (Basque Country, Spain).

Cognitive testing

A total of 455 children were assessed by the same psychologist at one year of age using the BL scale. This scale provides a value for the developmental age of the child and a global developmental quotient, as well as sub-scores for the various domains explored [12].

Subsequently, two clinical psychologists re-assessed 289 of the aforementioned children at this stage using WISC-IV scale. This scale evaluates overall cognitive ability and four specific domains of intelligence. Scores between 90 and 110 are considered to be normal [13].

To study intellectual results, we compared three subgroups of children. We established a control subgroup composed of those born of women who had UIC > 150 μg/L and FT4 > 10th percentile as well as being TPO-Ab negative in both trimesters. The remaining children were divided into two subgroups according to the FT4 levels: subgroup 1 was formed by those born to mothers with FT4 below the 10th percentile, and subgroup 2 included the rest.

Data analysis

Assuming that the proportion of low intellectual development, in children born from mothers with gestational hypothyroidism not adequately treated, is 15% [14], we calculated that 196 children had to be included to achieve an accuracy of 5.0% (confidence interval asymptotic normal bilateral 95.0%). As the expected percentage of dropouts is 10.0% we considered to recruit a minimum of 218 children in the study.

Qualitative data were expressed as percentages, and quantitative variables as means and standard deviations. Pearson's and

Table 2
Recruitment process.

	Included	Excluded
Random recruitment on children's first birthday	512	
Initial exclusion criteria		
Multiple gestation		19
Birth at less than 37 weeks and/or birth weight less than 2500 g		34
Serious health problem in the first year of life		4
Children who completed the Brunet-Lézine scale	455	
Random recruitment between 6 and 8 years of age	293	
Exclusion: pervasive developmental disorder diagnosed		4
Children who completed the WISC-IV	289	