



Intellectual performance of children of mothers with an untreated thyroid disorder in the first trimester of pregnancy

Sprawność intelektualna dzieci matek z nieleczoną chorobą tarczycy w pierwszym trymestrze ciąży

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Abstract

Introduction: The focus of the present study was the importance of the mother's thyroid function for foetal development in the first trimester, when the baby is totally dependent on the mother for thyroid hormones.

Materials and methods: The study consisted of testing the intellectual performance of children with both euthyroid and thyroid-dysfunction mothers. The experimental group comprised 60 children of mothers with an untreated thyroid disorder in the first trimester of pregnancy (TSH ≥ 3.5 mIU/L [standard 0.15–3.5] and/or TPO-Ab ≥ 20 IU/L [standard < 20]). The control group contained 132 children whose mothers showed no symptoms of a thyroid disorder either before or during pregnancy/postpartum. Both groups of children were administered the Wechsler Intelligence Scale for Children — Third Edition (WISC-III), whereby the intellectual performance of the experimental-group children was compared with that of the control-group children. The comparison included the percentage of children with IQ ≤ 85 and SLD and/or ADD risks. Our research is a follow-up to a blanket thyroid screening of 1649 pregnant women conducted during 2004–2006 in the region around Havlíčkův Brod.

Results: The research found no significant difference between the two groups of children with respect to their intellectual abilities, either regarding their overall IQ ($p = 0.67$), verbal IQ ($p = 0.81$), performance IQ ($p = 0.41$), or the individual scores (VCI: $p = 0.85$; POI: $p = 0.54$, FDI: $p = 0.57$; PSI: $p = 0.13$), nor did the experimental group show a significantly higher occurrence of children with IQ ≤ 85 than the control group ($p = 0.66$). However, the experimental group did exhibit a statistically significant increase in the percentage of children with a suspected SLD or clinically significant attention issues ($p = 0.05$).

Conclusion: Untreated thyroid disorders in the first trimester of pregnancy can increase the risk of the child developing attention or learning issues. (*Endokrynol Pol* 2018; 69 (3): 241–245)

Key words: intelligence, specific learning disorders (SLD), attention-deficit disorders (ADD), pregnancy, thyrotropin, thyroperoxidase antibodies

Streszczenie

Wstęp: W niniejszej pracy skupiono się na znaczeniu funkcji tarczycy matki dla rozwoju płodu w pierwszym trymestrze ciąży, gdy dziecko jest całkowicie zależne od matki pod względem hormonów tarczycy.

Materiał i metody: Badanie polegało na sprawdzeniu sprawności intelektualnej zarówno dzieci matek z eutyreozą, jak i dzieci matek z dysfunkcją tarczycy. Grupa eksperymentalna składała się z 60 dzieci matek z nieleczoną chorobą tarczycy w pierwszym trymestrze ciąży (TSH $\geq 3,5$ mIU/l [norma 0,15–3,5] i/lub TPO-Ab ≥ 20 IU/l [norma < 20]). Grupa kontrolna obejmowała 132 dzieci, których matki nie przejawiały symptomów choroby tarczycy przed lub podczas ciąży/po porodzie. W obu grupach dzieci przeprowadzono Test Inteligencji Wechslera dla Dzieci, edycja trzecia (*Wechsler Intelligence Scale for Children, Third Edition*), w którym porównano sprawność intelektualną dzieci z grupy eksperymentalnej ze sprawnością dzieci z grupy kontrolnej. Porównanie obejmowało odsetek dzieci z IQ ≤ 85 oraz ryzykiem SLD i/lub ADD. Prezentowane badanie stanowi kontynuację badań przesiewowych tarczycy przeprowadzonych w grupie 1649 kobiet w ciąży w latach 2004–2006 w regionie wokół Havlíčkův Brod.

Wyniki: Przeprowadzone badanie nie wykazało znaczącej różnicy między dwiema grupami dzieci, biorąc pod uwagę ich zdolności intelektualne dotyczące zarówno ogólnego wyniku IQ ($p = 0,67$), IQ w skali słownej (*verbal IQ*) ($p = 0,81$), IQ w skali bezsłownej (*performance IQ*) ($p = 0,41$) czy też wyniki indywidualne (VCI: $p = 0,85$; POI: $p = 0,54$, FDI: $p = 0,57$; PSI: $p = 0,13$), jak również w grupie eksperymentalnej nie wykazano znacząco wyższego występowania dzieci z IQ ≤ 85 w porównaniu z grupą kontrolną ($p = 0,66$). Niemniej, w grupie eksperymentalnej odnotowano statystycznie znaczący wzrost odsetka dzieci z podejrzeniem SLD lub klinicznie znaczącymi problemami z uwagą lub uczeniem się ($p = 0,05$).

Wnioski: Nielezione choroby tarczycy w pierwszym trymestrze ciąży mogą spowodować wzrost ryzyka rozwinięcia się u dziecka problemów z uwagą lub uczeniem się. (*Endokrynol Pol* 2018; 69 (3): 241–245)

Słowa kluczowe: inteligencja, specyficzne trudności w uczeniu się (SLD), zespół nadpobudliwości psychoruchowej (ADHD), ciąża, tyreotropina, przeciwciała przeciwko peroksydazie tarczycowej



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Introduction

The connection between neurodevelopmental disorders and thyroid dysfunction has been well-known for over a century. However, it was not until the end of the 20th century that the importance of the mother's thyroid hormones for foetal development was established [1]. It took another 10 years to reach a general agreement regarding the impact of thyroid hormone levels in pregnant mothers on foetal CNS development during the second and third trimesters. However, the importance of the mother's thyroid function for foetal development in the first trimester, when the baby is totally dependent on the mother for thyroid hormones, remained unclear.

The last two years saw the emergence of research works that highlighted the influence of thyroid hormone levels in pregnant mothers on the neuropsychological development of the foetus [2–5]. Because of the diverging results of the above studies and the absence of similar research in the Czech Republic, we decided to contribute to the world knowledge base on the topic and study the intellectual performance of children of mothers who showed symptoms of a thyroid disorder in the first trimester of pregnancy but did not start substitution treatment until the second trimester. Our work is a follow-up to a blanket screening for thyroid dysfunction in pregnant women conducted in 2004–2006 in the region around Havlíčkův Brod, when a total of 1649 thyroid examination results were collected [6].

The results of the present study are to provide information on the possible negative effects of thyroid dysfunction in pregnancy on foetal CNS development.

Material and methods

Material

There were two research groups consisting of children aged 6–9 years and their mothers. The experimental sample comprised 60 children of mothers with an untreated thyroid disorder in the first trimester of pregnancy ($TSH \geq 3.5$ mIU/L and/or $TPO\text{-}Ab \geq 20$ IU/L), and the control sample contained 132 children whose mothers showed no symptoms of a thyroid disorder either before or during pregnancy/postpartum.

The average age of children in the experimental group ($n = 60$) was 7.32 years ($SD 0.75$), and there were 37 boys and 23 girls in the group. The average age of children in the control group ($n = 132$) was 8.01 years ($SD 0.79$), and the group consisted of 67 boys and 65 girls.

Initially, it was planned to use the results of a blanket screening for thyroid dysfunction in pregnant women conducted from 1st January 2004 to 31st August 2008 in the region around Havlíčkův Brod [6]. The screen-

ing included thyroid stimulating hormone (TSH) and thyroid peroxidase antibody (TPO-Ab) tests in 2948 pregnant women on their first visit to a gynaecologist. The number represents 76.9% of the pregnant women from the above region, who delivered their babies during the given period in the maternity ward of the Havlíčkův Brod Hospital.

The screening period was chosen so that the children would be between six and nine years of age at the time when the Wechsler Intelligence Scale for Children — Third Edition (WISC-III) for children between the ages of 6 and 16 years, was administered. Of the 2948 pregnant women who underwent screening, 1649 were to deliver between 1st January 2004 and 31st August 2008. A total of 317 women had either newly detected subclinical hypothyroidism ($TSH \geq 3.5$ mIU/L), clinically manifest hypothyroidism ($TSH \geq 5.0$ mIU/L), and/or increased clinical levels of antibodies ($TPO\text{-}Ab \geq 20$ IU/L). The medium value of the stage of pregnancy at blood serum draw was 10 weeks. Due to procedural delays, treatment was not started until the second trimester of pregnancy. Of the 317 women with abnormal thyroid hormone levels, 19 miscarried and 11 moved out of the region. There were 46 women in the remaining group who refused to cooperate and did not appear for treatment, either during pregnancy or afterwards. Therefore, the final sample contained 241 women with a thyroid dysfunction during pregnancy, who could be invited to have their children tested; however, most of them ignored the invitation. Therefore, we addressed women followed-up by the Department of Endocrinology of the Havlíčkův Brod Hospital and at Parents' Evenings held by primary schools. A total of 267 children were tested, of whom 112 had mothers with a thyroid dysfunction during pregnancy, and 155 formed an initial control group. The data collection was performed from October 2012 to October 2013 by a single psychologist.

From the initial experimental group of 112 children, only 60 children (24.9%) were chosen to comprise the final experimental group. We excluded children whose mothers had a thyroid dysfunction in pregnancy but their TSH and TPO-Ab values in the first relevant trimester were normal because they started treatment previously (e.g. after a miscarriage), and children whose mothers were only diagnosed with a thyroid dysfunction in the second or third trimester and first-trimester data are not available. Also, 14 children were excluded from the experimental group, whose mothers did not respond to the invitation for treatment and, as a result, their thyroid dysfunction was left untreated throughout their pregnancy. The remaining 60 children had mothers with a provable thyroid dysfunction in the first trimester of pregnancy, who did not start treatment until the second trimester.

Table I. Parents' education

Tabela I. Wykształcenie rodziców

	Primary		Secondary		University	
	Mothers	Fathers	Mothers	Fathers	Mothers	Fathers
Experimental group	0	0	45	48	12	9
Control group	2	0	108	114	18	12

The initial control group consisted of 155 children; the refined control group contained 132 children. Some WISC-III results were excluded because no data were available on the mother's mid-pregnancy thyroid examination (these were either newly moved mothers or those who were not examined at the time of the screening).

The children's parents were administered an additional questionnaire to indicate their level of education (Table I). The questionnaire used the Czech educational system: primary education (nine years of education in total), secondary education (12 to 13 years of education in total), and university education.

The main criterion for inclusion into the experimental group was the mother's thyroid disorder in the first trimester of pregnancy. The thyroid disorders included subclinical or clinically manifest hypothyroidism (TSH ≥ 3.5 mIU/L) and/or increased clinical levels of thyroid peroxidase antibodies (TPO-Ab ≥ 20 IU/L, thyroiditis). The critical levels of TSH and TPO-Ab were established according to the used IRMA TSH kit (Immunotech, Beckman Coulter, Prague, Czech Republic) and a RIA TPO-Ab kit (same as above) at the time of screening [7]. Also, it was essential that treatment was not started until the second trimester. The control-group children all had clearly euthyroid mothers, who showed no symptoms of a thyroid disorder either during pregnancy or before/after.

Methods

A 2002 version of the WISC-III re-standardised for the Czech population was used. The scale provides scores for verbal IQ, performance IQ, and full IQ, and also four primary index scores, including the Verbal Comprehension Index, Perceptual Organisation Index, Freedom from Distractibility Index, and Processing Speed Index. Each testing was accompanied by a qualitative analysis to detect possible risks for an SLD or clinically significant attention issues. To perform the qualitative assessment, we utilised a discrepancy analysis developed by Kaufman and Lichtenberger [10]. Based on the above qualitative analysis, we could merely identify suspected SLDs or attention issues.

Thyroid function blood test

The TSH and TPO-Ab levels in the first-trimester pregnant women, who gave birth during the period of 1st January 2004 to 31st December 2006, were obtained during a blanket thyroid screening conducted by Špitálníková from 1st January 2004 to 31st August 2008 [6]. Blood draws were always done between 7 and 9 AM, with prior fasting. Serum samples were sent to the RIA laboratory of the Havlíčkův Brod Hospital, which is responsible for standard prenatal screening in the region. The samples were tested for TSH and TPO-Ab levels, for which an IRMA TSH kit (Immunotech, Beckman Coulter, Prague, Czech Republic) and a RIA TPO-Ab kit (same as above) were used.

Questionnaire for parents

The questionnaire was created to obtain the parents' and children's dates of birth and information regarding the parents' employment and the highest level of education achieved.

Results

The children whose mothers had an untreated thyroid disorder in the first trimester ($n = 60$) did not show a significantly lower ($p = 0.67$) overall intellectual performance than the control-group children ($n = 132$). Likewise, no statistically significant differences were found with respect to verbal IQ ($p = 0.81$), performance IQ ($p = 0.41$), or the individual scores (see Table II).

Also, no statistically significant differences were found between the two groups with respect to the occurrence of children with $IQ \leq 85$ ($p = 0.66$). There were nine out of 60 children with $IQ \leq 85$ in the experimental group and 23 out of 132 in the control group.

Using a qualitative analysis, we identified a total of 23 children with clinically significant deviations in intellectual performance, 14 in the experimental group ($n = 60$) and nine in the control group ($n = 132$). In the experimental group, there were two children with a suspected SLD (Specific Learning Disability) and 12 children with clinically significant attention issues, particularly verbal attention. In the control group, there were five children with a suspected SLD and

Table II. Intellectual performance of children with euthyroid as well as thyroid-dysfunction mothers; percentage of children with IQ ≤ 85; risk of SLD or ADD**Tabela II.** Sprawność intelektualna dzieci matek z eutyreozą, jak również dysfunkcją tarczycy; odsetek dzieci z IQ ≤ 85; ryzyko SLD lub ADHD

	Experimental group (n = 60)	Control group (n = 132)	Difference (95 % CI) (Control group — experimental group)	p-value
Mean full IQ	98.68 ± 13.05	97.86 ± 11.93	0.82 (–3.83 to 5.47)	0.67
Mean verbal IQ	96.92 ± 12.37	95.32 ± 11.45	1.60 (–2.81 to 6.01)	0.81
Mean performance IQ	100.95 ± 15.15	101.45 ± 13.71	0.50 (–4.87 to 5.87)	0.41
Mean VCI	98.20 ± 12.32	96.32 ± 11.42	1.88 (–2.53 to 6.29)	0.85
Mean POI	100.37 ± 14.91	100.15 ± 13.30	0.22 (–5.06 to 5.50)	0.54
Mean FDI	92.47 ± 14.68	92.09 ± 12.71	0.38 (–4.76 to 5.52)	0.57
Mean PSI	101.37 ± 15.05	104.11 ± 15.98	2.74 (–2.87 to 8.35)	0.13
IQ ≤ 85 (%)	15.00	17.42	2.42 (–3.33 to 8.17)	0.66
SLD/ADD (%)	23.33	6.82	16.5 (10.56 to 2.44)	0.05

four children with clinically significant attention issues. Children of mothers with an untreated thyroid disorder in the first pregnancy trimester showed a significantly higher occurrence of a suspected SLD or clinically significant attention issues ($p = 0.05$), particularly with respect to verbal comprehension, which is in line with the findings of other studies on the topic [7–9].

Discussion

Similarly to foreign-based studies with the same conception [2, 4], the objective of the present study was to test the intellectual performance of children aged six to nine years with both euthyroid and thyroid-dysfunction mothers. Use of the WISC-III made it possible to test not only the children's overall IQ, but also the verbal and performance IQ components and the four primary index areas (VCI, POI, FDI, PSI). We found no significant differences between a group of children of mothers with an untreated thyroid disorder in the first pregnancy trimester and a group of children whose mothers showed no symptoms of a thyroid disorder before, during, or after pregnancy. Some previous studies did find a link between low thyroid hormone levels or elevated clinical levels of thyroid peroxidase antibodies in pregnant women and impaired cognitive development of the children [2–4, 9, 11]; however, all of the above studies examined the intellectual performance of children whose mothers had an untreated thyroid disorder throughout their pregnancy. It is in this respect that our study differs. The group of women who declined treatment and agreed to have their children was too small to be used as a research sample ($n = 14$); the rest of the women with an untreated thyroid disorder showed no interest in participating in our research. The

size of the research sample, children's age group, the diagnostic methods, and the TSH criterion used make our research are comparable to a work by Haddow et al. [2], who, nevertheless, found a statistically significant difference between the experimental and the control groups. The difference could be connected to the outset of treatment in the second trimester in our study.

Because the study by Haddow et al. found a higher occurrence of below-average intelligence levels among the experimental group of children [2, 11], we decided to test the occurrence among our groups as well. The percentage of children with IQ ≤ 85 was comparable in both groups ($p = 0.66$). The fact that the women with thyroid dysfunction were treated in the second trimester of their pregnancy leads us to suggest that even delayed treatment may have positive effects on foetal CNS development.

Another focus of our research was the occurrence of specific learning disorders and attention deficiencies in children of mothers with a thyroid dysfunction during pregnancy. Numerous studies consider the mother's thyroxine levels essential for optimum neuropsychological development of the foetus, particularly in the first trimester of pregnancy [2, 4, 12]. Ghassabiane et al. [9], Haddow et al. [2], and other authors [7, 8] found an increased occurrence of specific learning disorders and suspected ADHDs in children of mothers with a thyroid disorder during pregnancy. Based on a qualitative analysis of all the WISC-III test results we identified a total of 14 children (23.33%) in the experimental group and nine (6.82%) children in the control group with a suspected SLD or clinically significant low verbal attention levels. The above difference has been found to be statistically significant ($p = 0.05$). However, there were no instances of a suspected attention deficiency

disorder as such. Suboptimal verbal attention is found not only in subjects with an attention deficiency disorder, but also in those unable to retain verbal symbols, which is related to a verbal attention component called encoding [13]. Verbal encoding depends on the amygdale and hippocampus and their interactions. Verbal attention issues are negatively reflected particularly in the Digit Span and Arithmetic sub-tests, and they can be expected to have a negative impact on the child's school performance. An untreated thyroid dysfunction in the first trimester of pregnancy thus appears to positively correlate with specific learning disorders and clinically significant verbal attention issues. To confirm the above connection and establish a diagnosis, further tests of the children's cognitive functions should be performed.

Similarly to previous studies on the same topic [2, 4], we compared the difference in intellectual performance between the experimental (thyroid-dysfunction) and the control group. The average scores for both groups were, using data from both foreign studies and our own research, found to be in the middle range. The negative impact of a first-trimester thyroid disorder on foetal CNS development appears to be local rather than global, and limited to certain parts of the CNS [14], which is reflected in a more frequent occurrence of cognitive function impairment [2, 15, 16]. According to Williams [17], thyroid hormones play an important part throughout the pregnancy. In the first trimester, maternal thyroid hormones are responsible for neural cell migration and differentiation. The second and third trimesters are characterised by the most turbulent foetal CNS development, with thyroid hormone-dependent processes such as neurogenesis, neural cell migration, axon growth, dendritic branching, and synaptogenesis. This is also when myelinisation and glial cell differentiation and migration start to occur.

We are aware of the limitations of our research, including the small sample size and possible occurrence of the second type of error. Nonetheless, studies with the same focus using comparable numbers of participants are no exception, and they have brought valuable information [2–4]. Also, we are aware of the bias that might have been caused by self-selective sampling, both at school level and at parent level.

We consider the main benefit of our research to be the utilisation of the full diagnostic potential of the WISC-III test. Because our research is the first of its kind in the Czech Republic, comparisons could be made only with foreign studies. We can conclude that our results

are in agreement with some of the foreign studies' findings, particularly concerning the more frequent occurrence of cognitive deficiencies among children of thyroid-dysfunction mothers in comparison with children of euthyroid mothers [9–11].

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