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Original Scientific Paper

THYROID DYSFUNCTION IN PREGNANCY: COMPARISON OF OUTCOMES IN INFANTS

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SUMMARY – The aim of this study was to compare the incidence of mild psychomotor delay in infants whose mothers were treated for thyroid dysfunction regardless of the cause during first trimester of pregnancy with those whose mothers did not use medications prenatally. The sample included 200 infants up to 4 months of age. Half of the infants were examined by a pediatric physiatrist, while the other half were chosen randomly from the primary pediatric clinic. Binary logistic regression was performed to assess the impact of factors on psychomotor delay. The model contained seven independent variables derived from bivariate analyses and clinical relevance. Results showed that the infant's chance of having psychomotor delay was 5.53 times higher if the mother had drug-compensated thyroid dysfunction. Younger gestational age increased the likelihood of delay 2.12 times *per* each gestational week. The likelihood of psychomotor delay also rose by 1% *per* 1 g of birth weight reduction. We found strong positive linear correlation between maternal drug-compensated thyroid dysfunction during pregnancy and psychomotor delay in infants, which has not been reported elsewhere. This differentiates an important and common prenatal risk factor and lays the foundation for faster initiation of habilitation of infants at risk. These insights provide a basis for planning the National Screening Program for Neurorisk Infants.

Key words: *Habilitation*; *Infants; Neurodevelopmental delay; Psychomotor delay; Thyroid dysfunction*

Introduction

According to Baker[1], psychomotor delay is a term describing infants who do not show the expected developmental properties according to their age. This includes neurodevelopmental, cognitive, emotional, and behavioral disorders. The number of children diagnosed with mild psychomotor delay has been increasing in recent decades. This delay has broad and serious adverse impacts on psychological and social well-being in infancy and childhood[1].

Although the causes remain unknown, numerous risk factors that can lead to mild or more severe delay of the psychomotor development of children have been differentiated, and they are divided into prenatal, perinatal, and postnatal. The most common risk factors include multiple pregnancy, gestational diabetes and hypertension, intrauterine growth restriction (IUGR) and preterm birth, cesarean delivery, low

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birth weight (<2500 g), and Apgar score less than 8[2,3]. If this deviation is not recognized and treated timely, it without exception leads to numerous motor and cognitive disorders. Therefore, it is important to identify infants with neurorisk factors as early as possible in order to prevent or reduce psychomotor delay by inclusion in the habilitation protocol. As early as 1970, epidemiological studies recognized the effect of untreated maternal thyroid dysfunction on the maturation and development of fetal brain, and it was also recognized as a common cause of abortion or fetal death[4]. Fetal brain is thought to be most sensitive to this delay in the period from 10th to 20th week of gestation, when a number of hormonal and morphological changes occur in response to increased metabolic requirements. Increased basal metabolism leads to accumulation of iodine in the thyroid gland, while hyperplasia and extensive vascularization of the thyroid gland result in its increase. During this period, fetal need for iodine is increased, while the kidneys are simultaneously more permeable to iodine, which is excessively lost in urine. All these changes are influenced by estrogen, which increases the amount of thyroxine-binding globulin and human chorionic globulin. The concentration of thyroxine-binding globulin reaches its maximum around 20th week of pregnancy and remains so by the end of pregnancy, with elevated total levels of triiodothyronine and thyroxine, while the concentration of free components of these hormones, which are metabolically active, remains unchanged, and pregnant women without thyroid dysfunction remain euthyroid.

Untreated maternal hypothyroidism during the first trimester of pregnancy is a well-known and clinically proven risk factor for psychomotor delay in infants[5]. This problem is accentuated by the fact that in early pregnancy stage, a large number of mothers are not yet aware of pregnancy, so prenatal diagnosis of this risk factor is insufficient and delayed.

A large number of studies have been performed on untreated pregnant women with thyroid dysfunction, and untreated clinical and subclinical hypothyroidism has been verified as a risk factor for psychomotor delay in children, but is also correlated with pregnancy-induced hypertension, preterm labor, fetal distress syndrome and low birth weight, and thus also indirectly correlated with psychomotor delay[6]. Batistuzzo and Ribeiro[7] conducted a systematic review of previous research, concluding that untreated clinical and subclinical maternal hypothyroidism during the first trimester of pregnancy leads to fetal cell differentiation disorders, inadequate central nervous system development, increased risk of perinatal complications, low birth weight, and impairment of cognitive and motor function in children. The same clinical effect was confirmed experimentally in rats, and arrest of cell differentiation, axonal growth, synaptogenesis and myelinization was detected as a mechanism of psychomotor deviations due to the lack of thyroid-stimulating hormone[7]. Smith *et al.*[8] included 20 pregnant women in their prospective study. They observed the effect of untreated thyroid dysfunction in mother in the first half of pregnancy on the neurological status of a child up to 2 years of age. This study proved that untreated subclinical hypothyroidism in the mother during the first half of pregnancy was associated with a lower mental developmental index in the first year of the child's life[8]. Haddow *et al.*[9] investigated the effect of elevated thyrotropin levels in 62 women during pregnancy, isolated or with decreased serum thyroxine levels, of which 48 pregnant women did not receive any therapy during the observed pregnancies. The authors compared the results of cognitive abilities in children aged 7 to 9 years, based on 15 cognitive tests. The results showed that unrecognized and untreated hypothyroidism during pregnancy was a risk factor for delayed cognitive abilities of children in early school age, and indicated the need to screen pregnant women for this deficit during pregnancy[9]. In 2016, Maraka *et al.*[10] systematically reviewed relevant databases and singled out 18 cohort studies which showed that compared to euthyroid pregnant women, pregnant women with untreated subclinical hypothyroidism had a higher risk of fetal loss (relative risk [RR] 2.01), placental abruption (RR 2.14) and early infant death (RR 2.58).

Summarizing the observations from our daily routine, we found that numerous mothers of infants diagnosed with psychomotor disorders during pregnancy were taking oral therapy to regulate thyroid dysfunction. There is a small number of methodologically relevant papers investigating the effect of drug-compensated maternal thyroid dysfunction on the onset of psychomotor delay, with non-uniform conclusions. Some studies showed that if maternal hypothyroidism was treated properly during pregnancy, it would have no side effect on the mother or developing fetus during or after pregnancy[11]. Rao *et al.*[12] conducted a systematic review and meta-analysis of relevant data-

bases, with the aim of detecting the effect of levothyroxine therapy on pregnancy outcome. Including 13 studies and 7970 subjects, they concluded that maternal levothyroxine therapy of subclinical hypothyroidism or autoimmune thyroid disease reduced the risk of preterm birth and pregnancy loss, but due to different outcomes depending on spontaneous or assisted onset of pregnancy, they emphasized the need for further research of this problem[12]. Based on their meta-analysis, Lee *et al.*[13] concluded that levothyroxine therapy in pregnant women with subclinical hypothyroidism and autoimmune thyroid disease led to a statistically significantly lower number of gestational diabetes, gestational hypertension, abortion, but had no effect on preeclampsia incidence. Unlike them, Maraka *et al.*[10] in their systematic review described one study that compared pregnancy outcomes of pregnant women on levothyroxine therapy with those without therapy and found no statistically significant difference in fetal loss risk, preterm birth, gestational hypertension, low birth weight or low Apgar score. Therefore, according to this study, the protective effect of levothyroxine therapy on the *noxa* caused by subclinical hypothyroidism has not been proven. This finding can be in indirect correlation with the onset of psychomotor delay, through other risk factors, but no direct correlation between psychomotor delay in infancy and levothyroxine therapy during pregnancy has been proven. Neither this nor other meta-analyses analyzed direct postnatal effects of drug-compensated maternal thyroid dysfunction, in the form of cognitive and motor abnormalities in infancy.

Therefore, the aim of this retrospective study was to compare the incidence of psychomotor delay in infants up to 4 months of age whose mothers were taking one of the oral thyroid dysfunction drugs during pregnancy with the incidence of the same delay in infants whose mothers were not on oral thyroid dysfunction therapy. This would differentiate another important and common prenatal risk factor for psychomotor disorder, which would lead to easier systematic triage of infants with potential deviations and their timely inclusion in the habilitation program in order to prevent the occurrence or reduce the deviation itself. Equally, a foundation for the development of the National Screening Program for Neurorisk Infants would be laid, which would ultimately result in reduction of the number of children with cognitive and motor impairments in preschool and school age.

Subjects and Methods

Design and participants

The study included 200 infants up to 4 months of age. The total number of respondents included 100 infants with a diagnosis of mild psychomotor delay confirmed by the pediatric physiatrist at Sestre milosrdnice University Hospital Center (UHC) and 100 infants with normal psychomotor development, confirmed by the primary pediatrician at Kruge Health Center (HC) in Zagreb.

Screening of infants was performed by examination, assessment of spontaneous and active movements, presence of pathologic movements and positions (qualitative analysis of general movements according to Prechtl, Hadders-Algri and Bobath), assessment of muscle strength and muscle tone, Vojta testing, palpation and passive mobility tests, and reflex tests. Infants who presented deviation from the assumed quality or quantity of any of the listed abilities during examination by the primary pediatrician at Kruge HC were referred for examination by the pediatric physiatrist at Sestre milosrdnice UHC; if the diagnosis of mild psychomotor delay was confirmed, infants were included in the test group. The infants that did not present deviation in terms of the described skills on examination by the primary pediatrician at Kruge HC were characterized as those with normal psychomotor development and thus were not referred for examination by the pediatric physiatrist and were not included in any habilitation program. These infants were included in the control group. Besides the diagnosis of mild psychomotor delay confirmed by pediatric physiatrist and infant age up to 4 months, another inclusion criterion was the mother taking oral medications to treat thyroid dysfunction during the first trimester of pregnancy. If during this period, the mother was taking other medications that may influence the onset of psychomotor delay in addition to thyroid dysfunction medications, the infant was excluded from the study. Likewise, if the pediatric physiatrist did not confirm the diagnosis of mild psychomotor delay, infants were also excluded from the study. To isolate other known risk factors resulting in the same delay, the collected data included maternal age at delivery, chronic maternal disease and other diseases during pregnancy, delivery mode, Apgar score, gestational age of the newborn, birth weight and length, possible IUGR, twin pregnancy, ultrasound of the newborn brain (with one intracerebral hemorrhage

grade 1, two intracerebral hemorrhage grade 2, and 0 infant without brain ultrasound), and infant age at the time of examination for the study. This study included pregnant women taking oral therapy during pregnancy to treat thyroid dysfunction, either hypothyroidism or hyperthyroidism regardless of the cause. All pregnancies were started naturally.

The sample of study subjects were collected randomly through a random number generator available at http://www.random.org/sequences/ during May 2020.

Ethics

During the study, the procedures were performed in line with ethical standards set by the responsible Committee on Human Experimentation of Sestre milosrdnice UHC and University of Kinesiology Ethics Committee No. 114/2016, and in accordance with the Helsinki Declaration as of 1975, as revised in 1983.

Statistical methods

Smirnov-Kolmogorov test was used to analyze data distribution. According to data size and distribution, appropriate non-parametric tests were used in all analyses. Categorical variables were expressed as frequencies and corresponding percentages, and quantitative variables by medians and interquartile range (IQR, 25th to 75th percentile). The χ^2-test was used to analyze differences in categorical clinical parameters between the groups with and without psychomotor delay. Fisher exact test or Fisher-Freeman-Halton exact test of independence when the contingency table is larger than 2x2 was used when there were less than 8 subjects *per* table cell. Mann-Whitney U test was

Table 1. Differences in the prevalence of categorical clinical variables between infants with (N=100) and without (N=100) psychomotor delay (χ^2-test)

		Without psychomotor delay		With psychomotor delay		p
		n	**%**	**n**	**%**	
Gender	Male	51	51.0	51	51.0	1.000
	Female	49	49.0	49	49.0	
Apgar score	4	0	0.0	1	1.0	0.031
	5	0	0.0	2	2.0	
	9	8	8.0	17	17.0	
	10	92	92.0	80	80.0	
Drug-compensated thyroid dysfunction of mother	No	90	90.0	67	67.0	<0.001
	Yes	10	10.0	33	33.0	
Overall risk factors (except for thyroid dysfunction)	No	70	70.0	68	68.0	0.760
	Yes	30	30.0	32	32.0	
Preterm infant	No	100	100.0	96	96.0	0.121
	Yes	0	0.0	4	4.0	
Twins	No	96	96.0	84	84.0	0.008
	Yes	4	4.0	16	16.0	
Gestational diabetes	No	83	83.0	86	86.0	0.558
	Yes	17	17.0	14	14.0	
Intrauterine growth restriction	No	100	100.0	92	92.0	0.007
	Yes	0	0.0	8	8.0	
Gestational hypertension	No	93	93.0	98	98.0	0.170
	Yes	7	7.0	2	2.0	
Delivery method	Vaginal	78	78.0	60	60.0	0.006
	Cesarean section	22	22.0	40	40.0	

used to analyze differences in quantitative variables between the groups.

Binary logistic regression was performed to assess the impact of a number of factors on the likelihood that patients have psychomotor delay. The model contained seven independent variables derived from previous bivariate analyses and clinical relevance. The level of statistical significance was set at $p<0.05$. Data analysis software system IBM SPSS Statistics, version 25.0 (https://www.ibm.com/analytics/spss-statistics-software, license grantee University of Zagreb, School of Medicine) was used on statistical analyses.

Results

Differences in the prevalence of categorical clinical variables between the infants with (N=100) and without (N=100) psychomotor delay are shown in Table 1. Pathologic Apgar scores (p=0.031), drug-compensated thyroid dysfunction of the mother (p<0.001), twin sibling (p=0.008), IUGR (p=0.007), cesarean section as delivery method (p=0.006) and pathologic neonatal ultrasound (US) findings (p<0.001) were significantly more common in the infants with psychomotor delay.

Table 2 shows differences in continuous clinical variables between the infants with and without psychomotor delay. Infants with psychomotor delay had significantly lower birth weight, birth length, gestational age (p<0.001 all), and age at study enrolment (p=0.013).

We performed a multivariate regression model (binary logistic regression) to assess the impact of several clinically and statistically important predictor variables in predicting allocation to the group with psychomotor delay (Table 3). Regression model was significant

Table 2. Differences in continuous clinical variables between infants with (N=100) and without (N=100) psychomotor delay (Mann–Whitney U test)

		Min	Max	Percentile			p
				25th	50th (median)	75th	
Maternal age (years)	Without psychomotor delay	19.00	39.00	28.00	32.00	35.00	0.360
	Psychomotor delay	18.00	47.00	28.00	32.00	36.00	
Birth weight (g)	Without psychomotor delay	2480.00	4210.00	3312.50	3530.00	3712.50	<0.001
	Psychomotor delay	1470.00	4120.00	2507.50	3130.00	3437.50	
Birth length (cm)	Without psychomotor delay	42.00	53.00	47.00	49.00	50.75	<0.001
	Psychomotor delay	38.00	55.00	45.00	47.00	49.75	
Gestational age (weeks)	Without psychomotor delay	37.86	40.71	38.89	39.86	40.14	<0.001
	Psychomotor delay	29.00	41.00	37.00	39.00	40.00	
Infant age at study enrolment (months)	Without psychomotor delay	2.13	4.57	3.03	3.13	3.63	0.013
	Psychomotor delay	3.00	4.87	3.17	3.42	3.88	

Table 3. Predicting allocation to the group with psychomotor delay (binary logistic regression)

R^2=44.1%; p<0.001	OR	95% CI		p
		Lower	Upper	
Infant age at enrolment in the study	1.11	0.48	2.59	0.804
Apgar score	0.99	0.45	2.14	0.974
Drug-compensated thyroid dysfunction of mother	5.53	2.29	13.31	<0.001
Birth weight (g)	0.99	0.98	0.99	0.001
Birth length (cm)	1.19	0.97	1.46	0.097
Gestational age (weeks)	0.47	0.29	0.78	0.003
Delivery method: vaginal	0.42	0.14	1.22	0.111

OR = odds ratio; 95% CI = 95% confidence interval

(p<0.001) and explained 44.1% of dependent variable variance (binary outcome: 0, without psychomotor delay and 1, psychomotor delay). Several predictor variables controlled for the effect of other variables in the regression model were significant, as follows: if the mother had drug-compensated thyroid dysfunction, the infant likelihood of having psychomotor delay was 5.53 times higher (odds ratio (OR)=5.53; 95% confidence interval (CI) 2.29-13.31; p<0.001). Younger gestational age also increased the likelihood of the infant having psychomotor delay by 1/0.47=2.12 times for each gestational week (OR=0.47; 95% CI: 0.29-0.78; p=0.001). Birth weight was also a significant predictor of psychomotor delay (OR=0.99; 95% CI: 0.98-0.99; p=0.003), indicating the likelihood of psychomotor delay to increase by 1% with 1 g of birth weight reduction.

Discussion

In this study, there was no statistically significant gender difference (p=1.000) between the two groups, but pathologic Apgar scores (p=0.031) were significantly more prevalent among infants with psychomotor delay. This result was expected because Apgar score lower than 8 is a well-known risk factor for neurocognitive and motor function delay in infants. Razaz *et al.*[14] included 33,883 children in their survey in order to assess the correlation between psychomotor development of children at 5 years of age and Apgar score at birth. They concluded that psychomotor delay was inversely associated with 5-minute Apgar score across its entire range[14]. Gestational diabetes and hypertension both are well-known risk factors for psychomotor delay in infancy, and these findings are consistent with research in children, where diabetic and high blood pregnancies have been found to impact motor and cognitive functions[15-17]. We found no statistically significant differences in these parameters between the two groups (p=0.558 for gestational diabetes and p=0.170 for gestational hypertension). Our findings showed that among infants with psychomotor delay, there were 4 times more twin siblings compared with the group of infants without psychomotor delay (p=0.008), which is consistent with numerous previous studies having reported that twin pregnancies often lead to psychomotor delay due to prematurity and low birth weight of infants[18,19]. In their study, Goetghebuer *et al.*[20] compared attainment of gross motor skills between the groups of twins and singletons, and concluded that twinning was an independent risk factor for psychomotor delay.

Cesarean birth is associated with lower cognitive and motor outcomes in childhood, and the cause is thought to lay in gut of cesarean-born child, which is seeded through contact with the mother's skin and hospital surfaces, unlike the vaginal-born child whose gut is colonized through the childbirth canal[21]. This difference in gut microbiota is observed until age 7 and is thought to send chemicals to the central nervous system, thus affecting cognitive and motor functions in the sensitive period of brain development[22,23]. Our result is consistent with previous studies, and among infants with psychomotor delay we found significantly more those having been delivered by cesarean section, compared with the group of infants without such delay (p=0.006). There is an indirect association that should also be taken into consideration, i.e., cesarean section is often used as a delivery method of choice in pathologic and complicated pregnancies, which are independent risk factors for psychomotor delay in infancy.

Another risk factor, proven by many studies so far, is IUGR. Our study showed that IUGR occurred more frequently in the group of children with psychomotor delay (p=0.007). IUGR is a condition that often causes psychomotor intellectual impairment[24-26], and this tends to worsen if associated with other proven risk factors such as low birth weight and birth length. Sacchi *et al.*[27] conducted a systematic review and meta-analyses that included 52,840 children, and concluded that children that had IUGR and were small for gestational age (both preterm and term children) had significantly poorer cognitive outcomes compared with children with age appropriate physical status at birth.

The results of our study indicate that low birth weight is a risk factor for psychomotor delay in infants and children, which is also confirmed by the literature. According to our results, the likelihood of psychomotor delay rises by 1% *per* 1 g of birth weight decrease. Similarly, numerous studies showed linear correlation between newborn birth weight decrease and the risk of psychomotor delay in infancy[28-30].

In our study, the mean gestational age was lower in the group of infants with psychomotor delay as compared with the group of infants without psychomotor delay (p<0.001). This result indicates that younger gestational age increases the likelihood of having

psychomotor delay 2.12 times for each gestational week, which is similar to the results reported by other recent studies[31]. Allotey *et al*. searched PubMed and Embase data bases and included 74 studies with more than 64,000 children. They found lower scores in motor skills, behavior, reading, mathematics, spelling and cognitive functions in preterm children[32]. Woythaler *et al*. concluded that preterm infants had increased odds for having physical and mental developmental delay compared with term infants[33]. Foulder-Hughes *et al*. proved that the degree of prematurity was in positive linear correlation with the results of cognitive and motor tests in children; so children with the lowest birth weight and gestational age had the lowest scores[34]. Filipouski *et al*. conducted a survey that included 125 very low birth weight preterm infants classified by the degree of birth weight and concluded that higher gestational age of low birth weight infants was associated to better neurodevelopmental outcome[35].

Our study showed that among infants with psychomotor delay, there were significantly more prevalent pathologic US findings ($p<0.001$), which is expected because newborns with psychomotor delay often have intracerebral hemorrhage caused by different types of perinatal *noxae*. In their study, Ment *et al*. showed that both environmental and genetic factors contributed to the risk of severe intraventricular hemorrhage in infancy[36].

The group of infants with psychomotor delay was statistically significantly younger at the time of enrolment in the study ($p=0.013$) as compared with the group of infants without any delay observed, so the children in whom psychomotor delay was not verified had more time to develop and manifest deviation than children in the other group, which reduced the possibility of subject misclassification in the groups.

We found no statistically significant difference in maternal age at the time of pregnancy between the two groups ($p=0.360$).

When analyzing overall risk factors (except for thyroid dysfunction), our findings showed no statistically significant difference in their prevalence between the two groups ($p=0.760$), indicating that the selection of subjects and their randomization was performed in accordance with the recommendations, and that differences between the groups in terms of psychomotor delay could be attributed to drug-compensated maternal thyroid dysfunction, which yielded a statistically significant difference between the groups.

We found strong positive linear correlation between maternal drug-compensated thyroid dysfunction during pregnancy and psychomotor delay in infants aged up to 4 months, and if the mother took oral drugs for thyroid dysfunction during pregnancy, the likelihood for the infant to have psychomotor delay in infancy increased 5.53 times (OR=5.53; $p<0.001$). To the best of our knowledge, no similar results have been reported elsewhere to date. The mechanism underlying this clinical observation remains unknown and yet to identify.

Our study suffered from some limitations, i.e., a single-center design and relatively small number of infants with psychomotor delay. The inability to verify adherence of pregnant women to prescribed therapy also precluded any definitive conclusions.

Conclusion

This research, conducted among 200 infants aged up to 4 months, indicated that drug-compensated thyroid dysfunction of mother in pregnancy could be considered as a risk factor for psychomotor delay in infants. To date, the potential pathophysiologic mechanism of drugs used in thyroid dysfunction treatment influencing neurocognitive functioning of infants remains hypothetical. Although further investigations are required, our results confirmed a drug-compensated thyroid dysfunction of mother as the most significant predictor of psychomotor delay in infant. The insights gained from this research provide solid foundations for planning the National Screening Program for Neurorisk Infants. Infants with identified risk factor should be included in one of the habilitation protocols, which will ultimately result in a reduced number of children with cognitive and motor delay in preschool and school age.

References

1. Baker RC. Pediatric Primary Care: Well-Child Care. Lippincott Williams and Wilkins Publishers: Philadelphia, PA, USA; 2001.
2. Laliani N, Tatishvili N. Structural features of perinatal risk factors and their complications contributing to the development of psychomotor delay. Georgian Med News. 2008;157:56-9.
3. Drozd-Dabrowska M, Trusewicz R, Ganczak M. Selected risk factors of developmental delay in Polish infants: a case-control study. Int J Environ Res Public Health. 2018;15:2715. doi: 10.3390/ijerph15122715.
4. Mead MN. Mother's thyroid, baby's health. Environ Health Perspect. 2004 Aug;112(11):A612. doi: 10.1289/ehp.112-a61.

5. Wasserstrum N, Anania CA. Perinatal consequences of maternal hypothyroidism in early pregnancy and inadequate replacement. Clin Endocrinol (Oxf). 1995;42(4):353-8. http://dx.doi.org/10.1111/j.1365-2265.1995.tb02642.x.
6. LaFranchi SH, Haddow JE, Hollowell JG. Is thyroid inadequacy during gestation a risk factor for adverse pregnancy and developmental outcomes? Thyroid. 2005;15(1):60-71. http://dx.doi.org/10.1089/thy.2005.15.60.
7. Batistuzzo A, Ribeiro MO. Clinical and subclinical maternal hypothyroidism and their effects on neurodevelopment, behavior and cognition. Arch Endocrinol Metab. 2020 Feb;64(1):89-95.
8. Smit BJ, Kok JH, Vulsma T, Briët JM, Boer K, Wiersinga WM. Neurologic development of the newborn and young child in relation to maternal thyroid function. Acta Paediatr. 2000;89(3):291-5.
9. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, *et al*. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med. 1999;341(8):549-55. doi: 10.1056/NEJM199908193410801.
10. Maraka S, Ospina NM, O'Keeffe DT, Espinosa de Ycaza AE, Gionfriddo MR, Erwin PJ, *et al*. Subclinical hypothyroidism in pregnancy: a systematic review and meta-analysis. Thyroid. 2016;26(4):580-90. doi: 10.1089/thy.2015.0418.
11. Tan TO, Cheng YW, Caughey AB. Are women who are treated for hypothyroidism at risk for pregnancy complications? Am J Obstet Gynecol. 2006:194(5):el-3. http://dx.doi.org/10.1016/j.ajog.2005.11.028.
12. Rao M, Zeng Z, Zhou F, Wang H, Liu J, Wang R, *et al*. Effect of levothyroxine supplementation on pregnancy loss and preterm birth in women with subclinical hypothyroidism and thyroid autoimmunity: a systematic review and meta-analysis. Hum Reprod Update. 2019;25(3):344-61. doi: 10.1093/humupd/dmz003.
13. Li J, Shen J, Qin L. Effects of levothyroxine on pregnancy outcomes in women with thyroid dysfunction: a meta-analysis of randomized controlled trials. Altern Ther Health Med. 2017;23(2):49-58.
14. Razaz N, Boyce WT, Brownell M, Jutte D, Tremlett H, Marrie RA, *et al*. Five-minute Apgar score as a marker for developmental vulnerability at 5 years of age. Arch Dis Child Fetal Neonatal Ed. 2016;101(2):F114-F120. doi: 10.1136/archdischild-2015-308458.
15. Cai S, Qiu A, Broekman BF, Wong EQ, Gluckman PD, Godfrey KM, *et al*. The influence of gestational diabetes on neurodevelopment of children in the first two years of life: a prospective study. PLoS One. 2016;11(9):e0162113. doi: 10.1371/journal.pone.0162113.
16. Nomura Y, John RM, Janssen AB, Davey C, Finik J, Buthmann J, *et al*. Neurodevelopmental consequences in offspring of mothers with preeclampsia during pregnancy: underlying biological mechanism *via* imprinting genes. Arch Gynecol Obstet. 2017;295(6):1319-29. doi: 10.1007/s00404-017-4347-3.
17. Letourneur A, Freret T, Roussel S, Boulouard M, Divoux D, Toutain J, *et al*. Maternal hypertension during pregnancy modifies the response of the immature brain to hypoxia-ischemia: sequential MRI and behavioral investigations. Exp Neurol. 2012;233(1):264-72. doi: 10.1016/j.expneurol.2011.10.014.
18. Brouwer SI, van Beijsterveldt TC, Bartels M, Hudziak JJ, Boomsma DI. Influences on achieving motor milestones: a twin-singleton study. Twin Res Hum Genet. 2006;9(3):424-30. doi: 10.1375/183242706777591191.
19. Ooki S. Motor development of Japanese twins in childhood as reported by mothers. Environ Health Prev Med. 2006;11(2):55-64. doi: 10.1007/BF02898143.
20. Goetghebuer T, Ota MO, Kebbeh B, John M, Jackson-Sillah D, Vekemans J, *et al*. Delay in motor development of twins in Africa: a prospective cohort study. Twin Res. 2003;6(4):279-84. doi: 10.1375/136905203322296629.
21. Polidano C, Zhu A, Bornstein JC. The relation between cesarean birth and child cognitive development. Sci Rep. 2017;7(1):11483. doi: 10.1038/s41598-017-10831-y.
22. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behavior. Nature Rev Neurosci. 2012;13:701-12. doi: 10.1038/nrn3346.
23. Diamond B, Huerta PT, Tracey K, Volpe BT. It takes guts to grow a brain: increasing evidence of important role of the intestinal microflora in neuro- and immune-modulatory functions during development and adulthood. Bioassays. 2011;33:588-91. PMID:21681774; http://dx.doi.org/10.1002/bies.201100042.
24. Puga B, Puga PG, de Arriba A, Armendariz Y, Labarta JI, Longas AF. Psychomotor and intellectual development (neurocognitive function) of children born small for gestational age (SGA). Transversal and longitudinal study. Pediatr Endocrinol Rev. 2009 Feb;6 Suppl 3:358-70. PMID:19404235
25. Murray E, Fernandes M, Fazel M, Kennedy SH, Villar J, Stein A. Differential effect of intrauterine growth restriction on childhood neurodevelopment: a systematic review. BJOG. 2015;122(8):1062-72. doi: 10.1111/1471-0528.13435.
26. Levine TA, Grunau RE, McAuliffe FM, Pinnamaneni R, Foran A, Alderdice FA. Early childhood neurodevelopment after intrauterine growth restriction: a systematic review. Pediatrics. 2015;135(1):126-41. doi: 10.1542/peds.2014-1143.
27. Sacchi C, Marino C, Nosarti C, Vieno A, Visentin S, Simonelli A. Association of intrauterine growth restriction and small for gestational age status with childhood cognitive outcomes: a systematic review and meta-analysis. JAMA Pediatr. 2020;e201097. doi: 10.1001/jamapediatrics.2020.1097.
28. Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics. 2009;124(2):717-28. doi: 10.1542/peds.2008-2816.
29. Fuentefria RN, Silveira RC, Procianoy RS. Neurodevelopment and growth of a cohort of very low birth weight preterm infants compared to full-term infants in Brazil. Am J Perinatol. 2018;35(2):152-62. doi: 10.1055/s-0037-1606351.
30. Kim HS, Kim EK, Park HK, Ahn DH, Kim MJ, Lee HJ. Cognitive outcomes of children with very low birth weight at 3 to 5 years of age. J Korean Med Sci. 2020;35(1):e4. doi: 10.3346/jkms.2020.35.e4.
31. Li X, Eiden RD, Epstein LH, Shenassa ED, Xie C, Wen X. Parenting and cognitive and psychomotor delay due to

small-for-gestational-age birth. J Child Psychol Psychiatry. 2017;58(2):169-79. doi: 10.1111/jcpp.12644.

32. Allotey J, Zamora J, Cheong-See F, Kalidindi M, Arroyo-Manzano D, Asztalos E, *et al*. Cognitive, motor, behavioural and academic performances of children born preterm: a meta-analysis and systematic review involving 64 061 children. BJOG. 2018;125(1):16-25. doi: 10.1111/1471-0528.14832.
33. Woythaler MA, McCormick MC, Smith VC. Late preterm infants have worse 24-month neurodevelopmental outcomes than term infants. Pediatrics. 2911 Mar;127(3):e622-e629. doi: 10.1542/peds.2009-3598.
34. Foulder-Hughes LA, Cooke RW. Motor, cognitive, and behavioural disorders in children born very preterm. Dev Med Child Neurol. 2003 Feb;45(2):97-103. PMID: 12578235.
35. Filipouski GR, Silveira RC, Procianoy RS. Influence of perinatal nutrition and gestational age on neurodevelopment of very low-birth-weight preterm infants. Am J Perinatol. 2013;30(8):673-80. doi: 10.1055/s-0032-1331030.
36. Ment LR, *Ådén* U, Bauer CR, Bada HS, Carlo WA, Kaiser JR, *et al*. Genes and environment in neonatal intraventricular hemorrhage. Semin Perinatol. 2015;39(8):592-603. doi: 10.1053/j.semperi.2015.09.006.

Sažetak

TIREOIDNA DISFUNKCIJA U TRUDNOĆI: USPOREDBA ISHODA U NOVOROĐENČADI

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Cilj istraživanja bio je usporediti učestalost blagog psihomotornog odstupanja dojenčadi čije su majke tijekom trudnoće uzimale lijek za disfunkciju štitne žijezde neovisno o uzroku s onima čije majke nisu rabile lijekove prije porođaja. Istraživanjem je obuhvaćeno 200 dojenčadi u dobi do 4 mjeseca. Polovinu ih je pregledao dječji fizijatar. Preostalih 100 ispitanika prikupljeno je nasumce iz ambulante primarne pedijatrijske skrbi. Metodom binarne logističke regresije procijenjen je utjecaj niza čimbenika na vjerojatnost nastanka psihomotornog odstupanja. Model je sadržavao sedam neovisnih varijabla kliničke važnosti dobivenih temeljem prethodno napravljenih bivarijatnih analiza. Provedenim je istraživanjem dokazana 5,53 puta veća vjerojatnost nastanka blagog psihomotornog odstupanja dojenčeta ako je majka imala lijekom kompenziranu disfunkciju štitnjače tijekom trudnoće. Niža gestacijska dob povećava vjerojatnost nastanka odstupanja 2,12 puta za svaki gestacijski tjedan. Takodjer, za 1 g smanjene porođajne težine vjerojatnost psihomotornog odstupanja raste za 1%. Ovom je studijom potvrđena snažna pozitivna linearna korelacija između lijekovima kompenziranog poremećaja rada štitnjače majke tijekom trudnoće i blagog psihomotornog odstupanja dojenčadi, što dosad nije drugdje zabilježeno. Diferencira se važan i čest prenatalni rizični čimbenik, što čini temelj za brži početak habilitacije rizične dojenčadi radi sprječavanja brojnih kognitivnih i motoričkih smetnja. Saznanja dobivena ovim istraživanjem mogu poslužiti kao osnova razvoja Nacionalnog programa probira neurorizične dojenčadi.

Ključne riječi: *Dojenče; Habilitacija; Neurorazvojni poremećaj; Psihomotorno odstupanje; Tireoidna disfunkcija*