

GADOMSKA, Anna, KUREK, Justyna, GORZYŃSKI, Rafał, GARSTKA, Michał, DOMINIK, Hanna, CZUDY, Zuzanna, PAWĘSKA, Wojciech, MOLCZYK-SIĘNCZAK, Justyna, RADWAŃSKI, Jan and POLATOWSKA, Marika. Hypothyroidism in pregnancy - a review. *Journal of Education, Health and Sport*. 2023;36(1):82-94. eISSN 2391-8306. DOI <http://dx.doi.org/10.12775/JEHS.2023.36.01.009> <https://apcz.umk.pl/JEHS/article/view/44877> <https://zenodo.org/record/8206655>

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 17.07.2023 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences). Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 17.07.2023 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

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The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 02.07.2023. Revised:30.07.2023. Accepted: 31.07.2023. Published: 08.08.2023.

Hypothyroidism in pregnancy - a review

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ABSTRACT

Introduction: Thyroid diseases, right after diabetes, are the most common endocrine disorder in pregnant women. Hypothyroidism occurs most frequently among all of the thyroid dysfunctions. Thyroid hormones are essential for the proper course of pregnancy and correct fetal development. Even a mild deficiency carries the risk of complications for both mother and child. It is therefore important to make a swift diagnosis, implement appropriate substitution treatment and monitor the course of the disease throughout pregnancy and in the postpartum period.

Purpose of the work: The article reviews the current state of knowledge regarding maternal hypothyroidism in pregnancy. The aim of the review is to highlight the prevalence of the disease, stress the associated adverse outcomes and present the recommended management.

Materials and methods: A literature research on PubMed, Cochrane Library and Google Scholar databases was done up to May 2023 with restriction to English and Polish language articles regarding hypothyroidism and pregnancy.

Summary: It is extremely important to perform TSH screening tests in women planning pregnancy and during the first obstetric visit. Due to the prevalence of thyroid disorders in society, it is necessary to educate both patients and physicians. An uncomplicated diagnosis process, low cost of screening tests and available treatment methods are able to prevent the often tragic consequences of maternal hypothyroidism.

Key words: overt hypothyroidism, subclinical hypothyroidism, pregnancy, adverse fetal outcomes

Introduction

Thyroid diseases, right after diabetes, are the most common endocrine disorder in pregnant women. Hypothyroidism occurs most frequently among all of the thyroid dysfunctions. Thyroid hormones are essential for the proper course of pregnancy. Even a mild deficiency carries a risk of complications for both mother and child. Especially at the stage of an early pregnancy - a critical period for the correct development of the fetal nervous system. It is therefore important to make a swift diagnosis, implement appropriate substitution treatment and monitor the course of the disease throughout pregnancy and in the postpartum period.

Change in thyroid physiology during pregnancy and iodine prophylaxis

Pregnancy is a period of increased demand for thyroid hormones (TH), which directly translates into an increased demand for iodine. Significant changes occur in the body of a pregnant woman when it comes to management of this microelement, as well as the production and metabolism of hormones. To prevent the development of hypothyroidism, the maternal thyroid gland must adapt to the following physiological changes.

Along with the increasing concentration of estrogens from early weeks of pregnancy, there is an increase in the concentration of TBG (thyroxine binding globulin), the main TH transporting protein in the blood. Estrogens directly stimulate the globulin synthesis and also induce the sialylation of TBG, which leads to a decrease in its hepatic clearance. [1] An increase in TBG translates into an increase in the concentration of total TH, but a decrease in their free fraction. This in turn enhances further TH production.

The placenta is responsible for the synthesis of human chorionic gonadotropin (HCG). Its concentration increases from the beginning of pregnancy and reaches its peak value around the 10-12th week. HCG shows structural and functional similarity to TSH (thyroid stimulating hormone) - it stimulates the thyrotropin receptor, which results in elevated TH production. In accordance with the negative feedback mechanism, there is a decrease in TSH levels in the first trimester of pregnancy. [2,3]

The processes mentioned above result in different reference values of hormones related to the functioning of the thyroid gland in the period of pregnancy, compared to the population norms. These values also vary by trimester.

During pregnancy, there is an increase in GFR (glomerular filtration rate), which results in an increase in the renal clearance of iodine. This leads to a decrease in the concentration of iodine in the serum, additionally intensified by the transfer of this microelement to the fetal-placental unit. [4] That, together with the increased production of TH during pregnancy, contributes to a higher demand for iodine. The model of prophylaxis used in Poland, based on the iodization of table salt, is insufficient. [5,6] It is therefore necessary to supplement this microelement in pregnant and lactating women. The daily intake of iodine should be 250 µg, which in Polish conditions corresponds to 150-200 µg of iodine in the form of supplements. [7] Deficiency of this micronutrient is a risk factor for the development of goiter and hypothyroidism in both mother and fetus.

Fetal thyroid development and the role of the placenta

The fetal thyroid develops from the endodermal cells of the floor of the pharynx. Around the 7th week of gestation it reaches its physiological position - anterior to the trachea. From the 12th week, the process of active iodine uptake begins. Around the 14th week, the fetal thyroid is capable of synthesizing trace amounts of thyroxine. A significant level of T4 is produced only around 18-20th week of gestation. Thyrotropin receptors located on the surface of thyrocytes begin to respond to TSH around the 20th week. The full efficiency of the hypothalamic-pituitary-thyroid axis is achieved only after birth. [8]

The fetus benefits from maternal TH throughout the whole pregnancy, but is completely dependent on them in the first trimester. It is a period of intensive organogenesis and development of the central nervous system. From 2nd to 5th month of gestation, TH supplied by the mother's organism affect the processes of proliferation, migration and organization of neurons. [9,10]

The placenta actively participates in maintaining correct hormonal balance - it regulates the proper supply of iodine, FT4 and FT3 to the fetus. In case of reduced availability of TH, there is an increase in activity of placental 5'-deiodinase type II, responsible for the conversion of T4 to T3. In turn, placental 5'-deiodinase type III, which is involved in the conversion of T4 to rT3 and T3 to T2 - forms with low metabolic activity, protects against excess thyroxine.

[11] The transport of iodides across the placenta is carried out by the sodium-iodine symporter present in the villi, as well as by diffusion due to a concentration gradient. [12] Therefore, an insufficient supply of iodine in the mother results in its deficiency in the child. The placenta is also permeable to antithyroid antibodies and antithyroid medication. Maternal TH pass to the fetus in small amounts.

Epidemiology, etiology

Three states of thyroid hormones deficiency can be distinguished in pregnant women:

1. Overt hypothyroidism (OH) - elevated TSH with decreased FT4 level (0.3-0.5% of pregnant women)
2. Subclinical hypothyroidism (SCH) - elevated TSH with normal FT4 level (2-3% of pregnant women)
3. Isolated hypothyroxinemia (IH) - decreased FT4 with normal TSH level (1-2% of pregnant women) [13,28]

The disorders are diagnosed based on reference values determined for each trimester of pregnancy.

Globally, iodine deficiency is the most common cause of hypothyroidism in pregnant women. A severe deficiency of this micronutrient can result in OH in both mother and fetus. [14] Isolated hypothyroxinemia is more common in areas of mild to moderate iodine deficiency. [15,16]

In developed countries and regions not affected by iodine deficiency, the main cause of hypothyroidism is chronic lymphocytic thyroiditis (Hashimoto's disease). [17] Studies conducted in the first half of pregnancy have shown the presence of anti-thyroid peroxidase antibodies (anti-TPO) in 70-90% of women with OH, 30-60% of women with SCH and about 10% of women with isolated hypothyroxinemia. [18]

Rarer causes of TH deficiency in pregnant women include: subtotal or total thyroidectomy, radioactive iodine treatment, history of head and neck radiotherapy, inappropriate use of antithyroid medication, inadequate TH replacement therapy or thyroid dysgenesis. [19]

Diagnosis

The diagnosis of hypothyroidism during pregnancy is different, not only because of the different reference ranges used. This is also due to the relatively low diagnostic value of clinical symptoms presented by pregnant women. There is an overlap of ailments that occur physiologically in healthy pregnancy with symptoms of hypothyroidism such as: weight gain, constipation or increased drowsiness. Therefore, the basis for the diagnosis of thyroid dysfunction in pregnant women is hormonal testing - serum TSH and FT4 levels.

PTE (Polish Society of Endocrinology) in the 2021 guidelines recommends routine measurement of TSH in pregnant women during the first obstetric visit. However, it does not recommend screening for free TH and antithyroid antibodies. If possible, it is suggested to assess thyroid function already during pregnancy planning. [7]

The aforementioned guidelines recommend screening for antithyroid antibodies in pregnancy only in specific cases: co-occurrence of autoimmune diseases - especially type 1 diabetes mellitus or a family history of these diseases, TSH levels > 2.5 mIU/l, thyroid ultrasound result suggestive of its autoimmune disease, co-occurrence of PCOS, history of postpartum thyroiditis, fertility issues, history of miscarriages and preterm births. [7]

The latest ATA (American Thyroid Association) guidelines recommend relating the obtained TSH, FT4 and FT3 results to the reference ranges set in the population for each trimester of pregnancy [20]. In Poland, these values were established on the basis of a prospective study involving a group of 172 pregnant women under the care of four different endocrinology centers (Krakow, Warsaw, Poznan, Bialystok). [Table 1.][21]

Trymestr	I	II	III
TSH (mIU/l)	0,009 - 3,18	0,05 - 3,44	0,11 - 3,53
FT3 (mIU/l)	3,63 - 6,55	3,29 - 5,45	3,1 - 5,37
FT4 (mIU/l)	11,99 - 21,89	10,46 - 16,67	8,96 - 17,23

Table 1. Reference ranges for the concentration of thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4) in particular trimesters of pregnancy in the Polish population. [21]

Treatment

The treatment for hypothyroidism in pregnant women is hormone replacement therapy with L-thyroxine. Medicaments containing liothyronine (T3) are contraindicated because the fetal CNS is relatively impermeable to T3. [7,20]

In patients with hypothyroidism who already receive L-thyroxine and plan on becoming pregnant, it is essential to measure TSH levels. It should be maintained between the lower limit of reference ranges and 2.5 mIU/l during the period of trying to conceive. For this reason, modification of the current dose may be required. [20]

In case of a suspected or confirmed pregnancy in a woman with hypothyroidism treated with replacement therapy, the dose of L-thyroxine should be increased by approximately 20-30%. [7,20]

If hypothyroidism is diagnosed during pregnancy, treatment should be started immediately with the estimated target dose to achieve euthyroidism as soon as possible. To determine it, the following scheme can be used [7,17]:

- TSH level 5–10 mIU/l → initial dose of L-thyroxine 25–50 µg/day;
- TSH level 10–20 mIU/l → initial dose of L-thyroxine 50–75 µg/day;
- TSH level > 20 mIU/l → initial dose of L-thyroxine 75–100 µg/day.

Treatment monitoring consists of measuring TSH levels in the first half of pregnancy every 4 weeks and at least once around 30th week of gestation. Adequate dosing of L-thyroxine is indicated by TSH levels remaining in the lower half of the trimester-specific reference ranges. [7,20]

TSH levels between 2.5 mIU/l and 3.18 mIU/l in the first trimester of pregnancy may suggest TH deficiency. The presence of antithyroid antibodies (aTPO, aTg) and a medical history, including family history, of autoimmune diseases are factors in favor of starting replacement therapy. If a decision is made not to start treatment with L-thyroxine, thyroid function should be monitored regularly. [7,20]

The isolated presence of antithyroid antibodies in patients planning pregnancy, as well as in those who are already pregnant, is not an indication for starting treatment. However, it is a risk factor for the development of hypothyroidism, therefore monitoring TSH levels is

recommended. In women planning pregnancy, TSH should be measured about 6 months before trying to conceive and also at the beginning of gestation. In pregnant women TSH should be measured every 4 weeks in the first half of pregnancy and at least once around 30th week of gestation. [7,20]

After giving birth most women may need to have their L-thyroxine dose reduced to the one used before pregnancy. For control, the TSH levels should be measured 6 weeks after the dose modification. In patients who started treatment during pregnancy and those on low doses of L-thyroxine (< 50 µg/day), discontinuation of treatment after delivery may be considered. [7,20]

Maternal hypothyroidism and adverse obstetric and neonatal outcomes

There is ample evidence that overt hypothyroidism in pregnant women is associated with a high risk of adverse obstetric outcomes such as: pre-eclampsia, spontaneous abortion, preterm delivery, premature placental abruption and postpartum haemorrhage. Adverse neonatal outcomes of maternal OH include: prematurity with its usual complications, low birth weight and RDS (respiratory distress syndrome). [22-26] A pregnant woman with hypothyroidism is at risk of developing anemia, gestational diabetes [27] and hypertension. Hypertension is detected in 22% of pregnant women with OH and 15% with SCH, compared to 7.6% of pregnant women without thyroid pathology. [28]

The degree of risk of complications associated with subclinical hypothyroidism in pregnant women is lower than in the case of overt hypothyroidism. However, there is a reported higher incidence of adverse obstetric outcomes such as: spontaneous abortion, premature placental abruption, preterm delivery or pre-eclampsia in women with SCH compared to euthyroid women. [23,29-31] A retrospective study by Casey et al. examined 17,298 women before the 20th week of gestation. They found that obstetric complications such as premature placental abruption and premature birth occurred 2-3 times more often in women with SCH compared to the control group. [29] Furthermore, a prospective study by Negro et al. showed a significantly higher risk of miscarriage in women without anti-TPO antibodies with SCH (TSH levels 2.5-5 mIU/L) compared to women with TSH levels < 2.5 mIU/L (6.1% vs. 3.6%). [30]

Impact of maternal hypothyroidism on child's neuropsychological development

The overriding aspect of hypothyroidism in pregnant women is impaired development of the fetal central nervous system. Mental abnormalities in children affected by maternal hypothyroidism can range from discrete IQ reductions to profound intelligence deficits. [32] Maternal TH are crucial for neuronal proliferation and migration early in pregnancy, when the fetus is not yet capable of synthesizing them on its own. From mid-pregnancy onward, TH from both mother and fetus play an important role in further neurogenesis, neuronal migration, synaptogenesis and myelination. [33,34]

Numerous studies have shown that even a mild deficiency of maternal TH can result in a child's neurocognitive impairment. In a historical study, Haddow et al. found that the offspring of mothers with untreated hypothyroidism during pregnancy scored an average of 7 points lower on IQ tests than the offspring of euthyroid mothers aged 7-9 years. [32] These children performed worse on all tests assessing intelligence, attention, speech, reading and visual-motor skills. A study by Li et al. analyzed the development of offspring of mothers affected by SCH or IH during the first trimester of pregnancy. Both groups scored lower on tests examining mental and psychomotor development. [35] Moreover, there are reports suggesting an increased risk of ADHD (attention deficit hyperactivity disorder) in children of mothers with hypothyroidism during pregnancy. [36]

Summary

Hypothyroidism in pregnancy carries the risk of adverse outcomes for both mother and fetus. Early detection of hypothyroidism and the implementation of replacement therapy make it possible to ensure adequate levels of thyroid hormones, essential for the correct course of pregnancy and child development. Therefore, it is extremely important to perform TSH screening tests in women planning pregnancy and during the first obstetric visit. Given the prevalence of thyroid disorders in society, it is necessary to educate both patients and physicians. An uncomplicated diagnosis process, low cost of screening tests and available treatment methods are able to prevent the often tragic consequences of maternal hypothyroidism.

Supplementary materials :

Table S1. Reference ranges for the concentration of thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4) in particular trimesters of pregnancy in the Polish population. [21]

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receiving funding : no funding was received.

All authors have read and agreed with the published version of the manuscript.

Financial support:

No financial support was received.

Conflict of interest:

The authors declare no conflict of interest.

References

- [1] Ain KB, Mori Y, Refetoff S. Reduced clearance rate of thyroxine-binding globulin (TBG) with increased sialylation: a mechanism for estrogen-induced elevation of serum TBG concentration. *J Clin Endocrinol Metab.* 1987 Oct;65(4):689-96. doi: 10.1210/jcem-65-4-689.
- [2] Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. *N Engl J Med.* 1994 Oct 20;331(16):1072-8. doi: 10.1056/NEJM199410203311608.
- [3] Glinoe D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev.* 1997 Jun;18(3):404-33. doi: 10.1210/edrv.18.3.0300.
- [4] Yazbeck CF, Sullivan SD. Thyroid disorders during pregnancy. *Med Clin North Am.* 2012 Mar;96(2):235-56. doi: 10.1016/j.mcna.2012.01.004.
- [5] Trofimiuk-Müldner M, Konopka J, Sokołowski G, et al. Current iodine nutrition status in Poland (2017): is the Polish model of obligatory iodine prophylaxis able to eliminate iodine deficiency in the population? *Public Health Nutr.* 2020; 23(14): 2467–2477. doi: 10.1017/S1368980020000403.
- [6] Zygmunt A, Adamczewski Z, Zygmunt A, et al. An assessment of the effectiveness of iodine prophylaxis in pregnant women—analysis in one of reference gynaecological-obstetric centres in Poland. *Endokrynol Pol.* 2015; 66(5): 404–411. doi: 10.5603/EP.2015.0050.
- [7] Hubalewska-Dydejczyk A, Trofimiuk-Müldner M, Ruchala M, Lewiński A, Bednarczuk T, Zgliczyński W, Syrenicz A, Kos-Kudła B, Jarząb B, Gietka-Czernel M, Szczepanek-Parulska E, Krajewska J, Andrysiak-Mamos E, Zygmunt A, Karbownik-Lewińska M. Thyroid diseases in pregnancy: guidelines of the Polish Society of Endocrinology [Choroby tarczycy w ciąży: zalecenia postępowania Polskiego Towarzystwa Endokrynologicznego]. *Endokrynol Pol.* 2021;72(5):425-488. doi: 10.5603/EP.a2021.0089.
- [8] Fuse Y. Development of the hypothalamic-pituitary-thyroid axis in humans. *Reprod Fertil Dev.* 1996;8(1):1-21. doi: 10.1071/rd9960001.
- [9] Morreale de Escobar G, Obregon MJ, Escobar del Rey F. Role of thyroid hormone during early brain development. *Eur J Endocrinol.* 2004 Nov;151 Suppl 3:U25-37. doi: 10.1530/eje.0.151u025.
- [10] Ausó E, Lavado-Autric R, Cuevas E, Del Rey FE, Morreale De Escobar G, Berbel P. A moderate and transient deficiency of maternal thyroid function at the beginning of fetal neocortico-genesis alters neuronal migration. *Endocrinology.* 2004 Sep;145(9):4037-47. doi: 10.1210/en.2004-0274.
- [11] Dentice M, Marsili A, Zavacki A, Larsen PR, Salvatore D. The deiodinases and the control of intracellular thyroid hormone signaling during cellular differentiation. *Biochim Biophys Acta.* 2013 Jul;1830(7):3937-45. doi: 10.1016/j.bbagen.2012.05.007.
- [12] Degrelle SA, Guibourdenche J, Galland F, Bidart JM, Fournier T, Evain-Brion D. Iodide transporters expression in early human invasive trophoblast. *Placenta.* 2013 Jan;34(1):29-34. doi: 10.1016/j.placenta.2012.11.002.
- [13] Sahay RK, Nagesh VS. Hypothyroidism in pregnancy. *Indian J Endocrinol Metab.* 2012 May;16(3):364-70. doi: 10.4103/2230-8210.95667.
- [14] Thilly CH, Delange F, Lagasse R, Bourdoux P, Ramioul L, Berquist H, Ermans AM. Fetal hypothyroidism and maternal thyroid status in severe endemic goiter. *J Clin Endocrinol Metab.* 1978 Aug;47(2):354-60. doi: 10.1210/jcem-47-2-354.
- [15] Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, Castagna MG, Mattina F, Violi MA, Crisà A, Artemisia A, Trimarchi F. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. *J Clin Endocrinol Metab.* 2004 Dec;89(12):6054-60. doi: 10.1210/jc.2004-0571.
- [16] Berbel P, Mestre JL, Santamaría A, Palazón I, Franco A, Graells M, González-Torga A, de Escobar GM. Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. *Thyroid.* 2009 May;19(5):511-9. doi: 10.1089/thy.2008.0341.
- [17] De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, Eastman CJ, Lazarus JH, Luton D, Mandel SJ, Mestman J, Rovet J, Sullivan S. Management of thyroid dysfunction during pregnancy and

- postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2012 Aug;97(8):2543-65. doi: 10.1210/jc.2011-2803. Erratum in: *J Clin Endocrinol Metab.* 2021 May 13;106(6):e2461.
- [18] Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RJ, Pulkkinen A, Mitchell ML. Prevalence of thyroid deficiency in pregnant women. *Clin Endocrinol (Oxf).* 1991 Jul;35(1):41-6. doi: 10.1111/j.1365-2265.1991.tb03494.x.
- [19] Cooper DS, Biondi B. Subclinical thyroid disease. *Lancet.* 2012 Mar 24;379(9821):1142-54. doi: 10.1016/S0140-6736(11)60276-6.
- [20] Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid.* 2017 Mar;27(3):315-389. doi: 10.1089/thy.2016.0457. Erratum in: *Thyroid.* 2017 Sep;27(9):1212.
- [21] Kostecka-Matyja M, Fedorowicz A, Bar-Andziak E, Bednarczuk T, Buziak-Bereza M, Dumnicka P, Górska M, Krasnodębska M, Niedźwiedzka B, Pach D, Ruchała M, Siewko K, Solnica B, Sowiński J, Szlachowska M, Trofimiuk-Müldner M, Wachowiak-Ochmańska K, Hubalewska-Dydejczyk A. Reference Values for TSH and Free Thyroid Hormones in Healthy Pregnant Women in Poland: A Prospective, Multicenter Study. *Eur Thyroid J.* 2017 Apr;6(2):82-88. doi: 10.1159/000453061.
- [22] Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, Faix JD, Klein RZ. Maternal thyroid deficiency and pregnancy complications: implications for population screening. *J Med Screen.* 2000;7(3):127-30. doi: 10.1136/jms.7.3.127.
- [23] Su PY, Huang K, Hao JH, Xu YQ, Yan SQ, Li T, Xu YH, Tao FB. Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: a prospective population-based cohort study in China. *J Clin Endocrinol Metab.* 2011 Oct;96(10):3234-41. doi: 10.1210/jc.2011-0274.
- [24] Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. *Thyroid.* 2002 Jan;12(1):63-8. doi: 10.1089/105072502753451986.
- [25] Davis LE, Leveno KJ, Cunningham FG. Hypothyroidism complicating pregnancy. *Obstet Gynecol.* 1988 Jul;72(1):108-12.
- [26] Leung AS, Millar LK, Koonings PP, Montoro M, Mestman JH. Perinatal outcome in hypothyroid pregnancies. *Obstet Gynecol.* 1993 Mar;81(3):349-53.
- [27] Karakosta P, Alegakis D, Georgiou V, Roumeliotaki T, Fthenou E, Vassilaki M, Boumpas D, Castanas E, Kogevinas M, Chatzi L. Thyroid dysfunction and autoantibodies in early pregnancy are associated with increased risk of gestational diabetes and adverse birth outcomes. *J Clin Endocrinol Metab.* 2012 Dec;97(12):4464-72. doi: 10.1210/jc.2012-2540.
- [28] Gietka-Czernel M. Cięża a choroby tarczycy. *Ginekologia po Dyplomie.* 2013;15(2): 46-58.
- [29] Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG. Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol.* 2005 Feb;105(2):239-45. doi: 10.1097/01.AOG.0000152345.99421.22.
- [30] Benhadi N, Wiersinga WM, Reitsma JB, Vrijkotte TG, Bonsel GJ. Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death. *Eur J Endocrinol.* 2009 Jun;160(6):985-91. doi: 10.1530/EJE-08-0953.
- [31] Wang S, Teng WP, Li JX, Wang WW, Shan ZY. Effects of maternal subclinical hypothyroidism on obstetrical outcomes during early pregnancy. *J Endocrinol Invest.* 2012 Mar;35(3):322-5. doi: 10.3275/7772.
- [32] Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med.* 1999 Aug 19;341(8):549-55. doi: 10.1056/NEJM199908193410801.
- [33] Haddow JE, McClain MR, Lambert-Messerlian G, Palomaki GE, Canick JA, Cleary-Goldman J, Malone FD, Porter TF, Nyberg DA, Bernstein P, D'Alton ME; First and Second Trimester Evaluation of Risk for Fetal Aneuploidy Research Consortium. Variability in thyroid-stimulating hormone suppression by human chorionic [corrected] gonadotropin during early pregnancy. *J Clin Endocrinol Metab.* 2008 Sep;93(9):3341-7. doi: 10.1210/jc.2008-0568. Epub 2008 Jun 10. Erratum in: *J Clin Endocrinol Metab.* 2008 Nov;93(11):4552.

- [34] Mohan V, Sinha RA, Pathak A, Rastogi L, Kumar P, Pal A, Godbole MM. Maternal thyroid hormone deficiency affects the fetal neocortico-genesis by reducing the proliferating pool, rate of neurogenesis and indirect neurogenesis. *Exp Neurol*. 2012 Oct;237(2):477-88. doi: 10.1016/j.expneurol.2012.07.019.
- [35] Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, Teng X, Guo R, Wang H, Li J, Chen Y, Wang W, Chawinga M, Zhang L, Yang L, Zhao Y, Hua T. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. *Clin Endocrinol (Oxf)*. 2010 Jun;72(6):825-9. doi: 10.1111/j.1365-2265.2009.03743.x.
- [36] Modesto T, Tiemeier H, Peeters RP, Jaddoe VW, Hofman A, Verhulst FC, Ghassabian A. Maternal Mild Thyroid Hormone Insufficiency in Early Pregnancy and Attention-Deficit/Hyperactivity Disorder Symptoms in Children. *JAMA Pediatr*. 2015 Sep;169(9):838-45. doi: 10.1001/jamapediatrics.2015.0498.