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Subclinical hypothyroidism in pregnant women in the iodine deficiency region: to treat or not to treat?

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Abstract. *Thyroid diseases occupy the top places in the structure of the endocrine pathology in recent years. According to the Ministry of Health of Ukraine, over the past 5 years the number of thyroid diseases has increased 5 times, and this indicator differs significantly in different regions of the country depending on a combination of environmental factors (remote stochastic effect of the Chernobyl accident, iodine deficiency, lifestyle, stress, malnutrition, micronutrient deficiencies, comorbidities, etc.). There is a close functional relationship between the thyroid and reproductive systems, which leads to a high probability of the development of combined disorders in one of these links of homeostasis. The problem of reproductive health disorders is of particular concern around the world and is relevant to the study of the nature of the effects of thyroid diseases on pregnancy. The prevalence and incidence of the thyroid disease vary in different regions of the country depending on the influence of environmental factors and their combination, one of which is iodine deficiency. The increasing number of stillborn infants, premature termination of pregnancy, infertility, deafness and strabismus of newborns, delayed physical, sexual and intellectual development of children, increasing cardiovascular diseases — this is not a complete list of negative effects of iodine deficiency on humans. The most common consequence of the iodine deficiency in pregnant women is subclinical hypothyroidism. Subclinical hypothyroidism is associated with many adverse events during pregnancy and with neonatal outcomes. The study of the peculiarities of the course of subclinical hypothyroidism in pregnant women in the iodine deficiency region today remains an urgent problem. This article presents an analysis of the publications of PubMed and Medline databases for the last decades.*

Keywords: *subclinical hypothyroidism; iodine deficiency; treatment*

Thyroid diseases occupy the first place among all endocrine pathologies today and remain one of the most difficult problems. According to the Ministry of Health of Ukraine, over the past 5 years the number of thyroid diseases has increased by 5 times, and this indicator significantly differs in different regions of the country depending on a combination of environmental factors (remote stochastic effect of the Chernobyl accident, iodine deficiency, lifestyle, stress, malnutrition, micronutrient deficiencies, comorbidities, etc.) [1, 2]. As of 1998, the incidence of the thyroid cancer in Ukraine (according to the Ukrainian standard) was 4.3 cases per 100 thousand inhabitants, and in 2016 this figure was 8.0 cases per 100 thousand people [3]. However, the incidence of a non-oncological thyroid pathology and its prevalence in Ukraine has also been increasing in recent decades.

For women of early reproductive age, in the structure of endocrine pathology thyroid disease occupies the first place in recent years. There is a close functional relationship between the thyroid and reproductive systems, which leads to a high probability of the development of combined disorders in disorders of one of these links of homeostasis. The problem of reproductive health disorders is of particular concern around the world and is relevant to study the nature of the impact of the thyroid disease on both fertility and pregnancy itself [4, 5].

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The effect of the thyroid gland on the reproductive system is realized both: through the peripheral endocrine glands (gonads and adrenal glands) and through the central structures (neurotransmitter and hypothalamic-pituitary system). Increased or decreased content of thyroid hormones alters the processes of steroidogenesis, affecting the gonads directly, as well as through the hypothalamic-pituitary system, thereby violating the mechanism of their relationship, especially the principle of negative feedback. The influence of the thyroid pathology on menstrual and reproductive function is explained by metabolic disorders (especially by a decreased metabolic activity in hypothyroidism), which change the sensitivity of receptor systems to hormonal influences at different levels of regulation [6].

The thyroid function is closely related to the hypothalamic-pituitary-ovarian system, primarily due to the presence of common central regulatory mechanisms. The thyroid gland is one of the most important parts of the neuroendocrine system and has a significant impact on the reproductive function. Disorders of the thyroid gland can cause premature or late puberty, menstrual disorders, anovulation, infertility, miscarriage, fetal pathology. In its turn, the state of the reproductive system has a pronounced effect on the thyroid function. It is confirmed by changes in the thyroid function during pregnancy and lactation, in benign tumors and hyperplastic processes of the female genital organs, in patients with dysfunctional uterine bleeding [7].

Equilibrium in the pituitary-thyroid system is due to the interaction of tropic hormones of the pituitary gland and effector endocrine glands. The enlargement of the thyroid gland, even is not accompanied by the absence of clinical signs, is an early sign of internal disorders, and often — at least minimal deficiency of thyroid hormones [8].

Thyroid hormones provide the realization of genetically inherited information into a specific human image (in the absence of the thyroid gland without the replacement therapy, the mental retardation develops). That is, no matter how ingenious the hereditary information from the ancestors of the child might be, in the absence of thyroid hormones, this will not be realized [9].

Luteinizing hormone (LH), follicle-stimulating hormone (FSH), human chorionic gonadotropin and thyroid stimulating hormone (TSH) are complex glycoproteins consisting of α- and β-subunits. The structure of the α-subunit of LH, FSH, chorionic gonadotropin and TSH is identical, and the β-subunit is specific for each hormone and determines its luteinizing, follicle-stimulating and thyroid-stimulating activity. Estrogens stimulate the thyroid function by intensifying the synthesis of thyroxine-binding globulin in the liver. Experimental studies have shown the presence of receptors for TSH and T3 in the ovary, which determines the possibility of a direct effect of thyroid dysfunction on steroidogenesis, ovulation, corpus luteum function [10].

Estrogens and thyroid hormones can alter the excretion of TSH and prolactin, affecting different levels of regulation of TRH formation and secretion and specific hormonal responses of the anterior pituitary gland. The imbalance of thyroid hormones can change the concentration of active steroids inside the target cells of the hypothalamus and pituitary gland, thus disrupting the mechanism of positive and negative feedback [10].

In diseases of the thyroid gland with an impaired thyroid function of the pituitary gland changes the production and synchrony of the release of TRH — one of the regulators of pulsating gonadotropin release.

Thus, the multilateral mechanism of the influence of the thyroid pathology on menstrual and reproductive functions of the woman is accurately defined. Alongside with it, there are differences in disorders of the reproductive system depending on the form of the thyroid pathology [4].

As it has already been mentioned, the prevalence and incidence of the thyroid disease vary in different regions of the country depending on the influence of environmental factors and their combination, one of which is iodine deficiency.

Iodine deficiency is an important medical and social problem in many countries around the world. According to the World Health Organization (WHO), pathological conditions associated with iodine deficiency rank third in the list of 38 most common non-communicable human diseases. According to WHO experts, one-third of the world's population belongs to the so-called "risk group" and is a potential target for the development of iodine deficiency diseases (IDD). The increasing number of stillborn babies, premature termination of pregnancy, infertility, deafness and strabismus of newborns, delayed physical, sexual and intellectual development of children, increasing cardiovascular disease — not a complete list of negative effects of "hidden hunger" on humans [11].

The iodine deficiency is a common natural phenomenon associated with iodine deficiency. It is calculated that in order to fully ensure the synthesis of TG and restore intra thyroid reserves, iodine should enter the human body in a stable amount, which depends on the age and functional state of the body [11].

The most common consequences of the iodine deficiency in pregnant women are subclinical hypothyroidism. Determination of TSH is a diagnostic marker of hyper- or hypothyroidism. Occasionally, the persistent hypothyroidism is caused by autoimmune thyroiditis (AIT) with elevated levels of antibodies to thyroid peroxidase (ATPO) or thyroglobulin, the consequences of surgical treatment, or radiation to the thyroid gland. Normal functioning of the thyroid gland is important for successful conception and pregnancy [12].

In a large prospective study of > 16,000 pregnant women with subclinical hypothyroidism, the risk of placental abruption and preterm birth was higher than in euthyroid women. In addition, their offspring were more likely to be admitted to the neonatal intensive care unit and had respiratory distress syndrome [13].

Other large studies comparing women with subclinical hypothyroidism and women with normal thyroid function during pregnancy have also demonstrated a link between subclinical hypothyroidism and miscarriage [14, 15], preterm birth [16, 17], and gestational diabetes [18], gestational hypertension [19, 20], eclampsia [19], premature placental abruption [21], intrauterine growth restriction and low birth weight [22].

The presence of TPO Ab appears to play a synergistic role with elevated TSH concentrations in increasing the risk of pregnancy complications. A recent large prospective study in China [23] found that pregnant women with higher TSH levels were 3.4 times more likely to have miscarriages than euthyroid women, and this risk tripled when these women also had positive TPO Ab levels.

Alternatively, two large prospective studies in the United States [24] and Finland [25] found no effect of subclinical hypothyroidism on pregnancy outcomes.

A meta-analysis [26] of 18 cohort studies examining 3,995 pregnant women with subclinical hypothyroidism found that pregnant women with subclinical hypothyroidism were twice as likely to lose pregnancy and were 2.6 times more likely to have stillbirths than women with normal thyroid function. They also had a higher risk of placental abruption and premature rupture of membranes. It was noted that the included studies had a low and moderate risk of accident, mainly due to limited representativeness of the studied samples, the lack of a significant difference in the evaluation of results.

Thyroid hormones are necessary for early brain development [27]. The mother's thyroid hormones are needed by the fetus until its own thyroid gland begins to function at ~ 14–18 weeks of gestation [28].

A retrospective study [29] reported that the IQ of children born to untreated, mostly mothers with overt hypothyroidism, was significantly lower than in children in the control group. However, the mean IQs did not differ significantly from those born to mothers who were treated (P = 0.20 and P = 0.90, respectively), although the treatment groups were small. Since then, several studies have reported that higher levels of maternal TSH during pregnancy may be associated with adverse effects on the neurocognitive functions of offspring [30, 31], while the others have not confirmed this [32, 33].

A recent meta-analysis [34], which included 11 observational studies, showed that compared to normal thyroid function, subclinical maternal hypothyroidism is associated with indicators of intellectual disability in offspring (odds ratio 2.14; 95% confidence interval, 1.20–3.83; P = 0.01).

In general, the conflicting results between the effects of subclinical hypothyroidism on the adverse effects of pregnancy may be partly explained by the different TSH cut-off values used in studies to determine subclinical hypothyroidism, taking into account TPO Ab+ and TPO Ab–. In addition, the thyroid function may change during pregnancy, and as a result, a woman diagnosed with subclinical hypothyroidism in early pregnancy may eventually develop overt hypothyroidism or spontaneously return to normal thyroid function [35].

If subclinical hypothyroidism is diagnosed during pregnancy, then despite well-developed clinical guidelines for the treatment of pregnant women with overt hypothyroidism [36], there has long been no consensus on whether to treat women with subclinical hypothyroidism. The American Congress of Obstetricians and Gynecologists in 2007 found insufficient evidence to recommend treatment for subclinical hypothyroidism during pregnancy [37].

At that time, American Thyroid Association (ATA) in 2011 issued recommendations for the treatment of pregnant women with SCH, but only when they have positive levels of TPO Ab [38]. One year later, the Endocrine Society published its recommendation for the general treatment of all pregnant women with subclinical hypothyroidism, recognizing that this recommendation was based on low evidence [39]. A recent evaluation of all clinical practice guidelines for the treatment of hypothyroidism during pregnancy [40] found that they differed and that the ATA (2017) guidelines ranked the highest overall, mainly due to the achievement of the goal and the highest performance in science, are strict and retain editorial independence. As a result, it was concluded that these guidelines need to be significantly improved.

The results of a prospective study [40] clearly informed in the guidelines published in 2011–2012. In this study, ~ 4,500 women were randomized to 11 weeks of gestation and underwent general screening for thyroid dysfunction based on the presence of risk factors for thyroid disease. All pregnant women were screened for thyroid dysfunction and initiated if confirmed. Of the dysfunction group, only high-risk women were screened, whereas the low-risk group was screened at the end of pregnancy; therefore, these women did not receive therapy. LT_4 therapy was initiated in hypothyroidism, which was detected at TSH > 2.5 mIU/l and a positive TPO Ab titer, so by definition, women with overt hypothyroidism were included, which was one of the limitations of the study. There was no significant difference between the total number of adverse events in the universal screening and the case detection group. Given only low-risk cohorts of women, complications were less likely to occur among women in the "universal screening" group than among women in the "case detection" group (OR 0.43; 95% CI 0.26–0.70) due to events that occurred. With unidentified and untreated patients with hypothyroidism (adverse effects were less likely with universal low-risk versus case detection, but no high-risk difference). However, the untreated group was significantly smaller (n = 34), so the study was not informative enough.

In a prospective study in China, LT_4 treatment was recommended for pregnant women with subclinical hypothyroidism [14]. Comparing 28 women who received treatment and 168 women who did not receive treatment, there was no difference in the rates of pregnancy loss (relative risk 0.46; CI 0.12–1.84), preterm birth (RR 0.31; CI 0.02–5.13), gestational hypertension (RR 3.00; CI 0.28–31.99), low weight at birth (RR 0.65; CI 0.04–11.71), or obtained a low score on the Apgar scale (RR 0.65; CI 0.04–11.71). This study was limited due to the small sample size, which led to inaccurate results.

In 2012, the results of the study of controlled antenatal thyroid screening were published [41]. This was a multicentre, randomized study where 21,846 women were randomized at ~ 12 weeks of gestation to the thyroid dysfunction group or to the control group. Treatment at a dose of 150 mcg LT_4 was started after 13 weeks of gestation, when women in the screening group were found to have TSH levels > 97.5 percentile, fT_4 < 2.5 percentile. The study did not reveal a difference in the IQ of children aged 3 years (in

the treated average IQ 99, in the control group IQ 100). The subgroup analysis, which included only women who met the criteria for subclinical hypothyroidism, had similar results. The study was criticised for the late start of LT_4 therapy (perhaps too late in pregnancy to affect brain development) and the relatively high, fixed dosage of LT_4. Moreover, the question was raised as to whether we could accurately estimate the IQ of a 3-year-old child.

A retrospective single-centre study [42] showed that LT_4 therapy in pregnant women with subclinical hypothyroidism was associated with a lower risk of low birth weight and a low Apgar score, but there was no statistically significant difference in other adverse effects of pregnancy and neonates. Although there is evidence of a number of potentially unclear factors, including socioeconomic and concomitant obstetric conditions, which allowed for an adjusted analysis, this study was limited by its retrospective nature and biased selection. In another study [43] lower chances of miscarriage and macrosomia were reported in pregnant women with subclinical hypothyroidism treated with LT_4 (RR 0.34; CI 0.21–0.56 and RR 0.46; CI 0.28–0,74 respectively). This study was also limited by its biased selection.

The results of the first national study in the United States have also been recently published [44]. Using a large database, 843 pregnant women with subclinical hypothyroidism treated with thyroid hormones were compared with 4562 women who did not take therapy. Treated women had a 38 % lower risk of losing pregnancy than untreated women. However, treatment with thyroid hormones has been associated with an increased risk of preterm birth, diabetes mellitus and preeclampsia. A stratified analysis by TSH groups showed that women treated with higher TSH levels had fewer pregnancy losses than those with lower TSH levels. This lack of benefit, together with the stated risk of side effects, has raised concerns about possible over-treatment of women with TSH between 2.5 and 4.0 mIU/l. This study was limited by its retrospective follow-up structure, lack of clinical details (eg, gestational age at the beginning of LT_4 therapy, TPO Ab status).

Another recent randomized study [45] showed that despite the lack of a beneficial effect of LT_4 therapy, to reduce preterm birth in women with subclinical hypothyroidism TPO Ab- and TSH from 2.5 to 10.0 mIU/l, it was found that LT_4 can reduce this complication (RR 0.38; 95% CI 0.15–0.98; P = 0.04).

Similarly, the Tehran Thyroid Study showed a 70 and 83 % reduction in preterm birth and neonatal hospitalization in pregnant women treated with LT_4 and TPO Ab+, respectively [46]. The effect of positive LT_4 treatment was observed mainly among TPO Ab+ women with TSH ≥ 4.0 mIU/l.

ATA recommends treatment of maternal hypothyroidism to establish maternal TSH concentrations < 2.5 mIU/l [47]. ATA also suggests repeating thyroid function tests at least every 4 weeks during the first half of pregnancy and again at least once about 30 weeks of pregnancy [47]. Alternatively, the European Endocrine Society proposes to repeat thyroid function tests every 4–6 weeks during pregnancy [39] and, like ATA, recommends adjusting the dose of LT_4 to maintain TSH levels within the target trimester ranges: I trimester — 0.1–2.5 μIU/ml, II trimester — 0.2–3.0 μIU/ml, III trimester — 0.3–3.0 μIU/ml.

After delivery, LT_4 should be reduced to the patient's previous dose. Additional testing of the thyroid function should be performed ~ 6 weeks after delivery [47]. For women who received LT_4 during pregnancy, LT_4 could potentially be discontinued, especially when the LT_4 dose is < 50 mcg. The decision to discontinue LT_4 should, if desired, be made by the patient and physician. If LT_4 is discontinued, serum TSH levels should be assessed after 66 weeks [47].

A retrospective single-centre study [42] showed that 54 % of pregnant women with subclinical hypothyroidism who started taking LT_4 discontinued treatment after delivery/miscarriage.

The first challenge for making recommendations for subclinical hypothyroidism is to determine the normal TSH ranges and to determine the level associated with adverse effects. Currently, most patients receive treatment using fixed threshold levels of TSH, which are determined by laboratories.

It is essential to conduct studies that can help clinicians prescribe therapy using appropriate control ranges.

Although randomized clinical trials that evaluate the effect of LT_4 therapy on the clinical outcomes of patients with subclinical hypothyroidism are available, the identification of patients in need of treatment remains a challenge, largely due to the limited nature of these studies.

One of the important limitations of these studies is the initiation of LT_4 therapy in the second trimester of pregnancy. It is believed that if LT_4 affects early adverse pregnancy outcomes (e.g., miscarriage), this therapy should be started as close as possible to conception. In addition, these studies included predominantly healthy patients; it is possible that those who are at greater risk of complications will benefit more from treatment [42].

To date, important predictors of adverse effects in patients with subclinical hypothyroidism have been identified, such as an autoimmune status of the thyroid gland and the degree of elevated TSH levels.

To improve the quality of evidence for the treatment of subclinical hypothyroidism during pregnancy, large multicentre randomized clinical trials are needed in which LT_4 treatment is started early, with pre-scheduled subgroup analysis based on the risk of complications to determine not only whether LT_4 therapy has a positive effect, but what patients are more likely to benefit from it. Although there is sufficient clinical data, little is known about the physiological mechanism by which mild thyroid dysfunction can lead to adverse pregnancy outcomes, or how LT_4 therapy will lead to better outcomes.

Subclinical hypothyroidism is associated with many adverse events during pregnancy and neonatal consequences. LT_4 treatment has been associated with better reproductive outcomes, reduced risk of pregnancy and preterm birth, in women using assisted reproductive technologies. However, well-conducted large randomized trials using LT_4 in early pregnancy and in the planning stage of pregnancy are still needed in this area [48, 49].

Analyzing the above-provided information, it can be argued that most studies do not reflect the gestational age at which hypothyroidism was diagnosed, there is no clear

data on which indicators and in which trimester titrated LT_4 replacement therapy. Also, the studies do not provide any data on whether pregnant women lived in iodine-deficient regions or not.

Therefore, the study of the peculiarities of the course of subclinical hypothyroidism in pregnant women in the iodine deficiency region today remains an urgent problem and requires further research.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Субклінічний гіпотиреоз у вагітних в йододефіцитному регіоні: лікувати чи ні?

Резюме. Захворювання щитоподібної залози в структурі ендокринної патології останнім часом посідають перші місця. За даними Міністерства охорони здоров'я України, за останні 5 років кількість захворювань щитоподібної залози збільшилась у 5 разів, причому даний показник суттєво відрізняється в різних регіонах країни залежно від сукупності чинників зовнішнього середовища (віддалений стохастичний ефект аварії на Чорнобильській АЕС, йодний дефіцит, спосіб життя, стрес, нераціональне харчування, недостатність мікроелементів, супутні захворювання тощо). При цьому відомий тісний функціональний взаємозв'язок тиреоїдної та репродуктивної систем, що зумовлює високу ймовірність розвитку поєднаних порушень при розладах однієї з цих ланок гомеостазу. Проблема порушень репродуктивного здоров'я зумовлює особливо серйозне занепокоєння у всьому світі та є актуальною щодо вивчення характеру впливу захворювань щитоподібної залози на вагітність. Показники захворюваності на патології щитоподібної залози та їх поширеності відрізняються в різних регіонах країни залежно від впливу чинників зовнішнього середовища та їх комбінації, одним із таких є дефіцит йоду. Збільшення кількості мертвонароджених немовлят, передчасне переривання вагітності, безпліддя, туговухість та косоокість новонароджених, затримка фізичного, статевого та інтелектуального розвитку дітей, зростання показників серцево-судинних захворювань — далеко не повний перелік негативного впливу йодного дефіциту на людину. Найбільш частими наслідками йодного дефіциту у вагітних є субклінічний гіпотиреоз. Субклінічний гіпотиреоз асоціюється з багатьма несприятливими подіями під час вагітності та неонатальними наслідками. Вивчення особливостей перебігу субклінічного гіпотиреозу у вагітних у йододефіцитному регіоні на сьогодні залишається актуальною проблемою. У статті наведений аналіз публікацій баз даних PubMed, Medline за останні десятиліття.

Ключові слова: субклінічний гіпотиреоз; йодний дефіцит; лікування

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Субклинический гипотиреоз у беременных в йододефицитном регионе: лечить или нет?

Резюме. Заболевания щитовидной железы в структуре эндокринной патологии в последние годы занимают первые места. По данным Министерства здравоохранения Украины, за последние 5 лет количество заболеваний щитовидной железы увеличилось в 5 раз, причем данный показатель существенно отличается в различных регионах страны в зависимости от совокупности факторов внешней среды (удаленный стохастический эффект аварии на Чернобыльской АЭС, йодный дефицит, образ жизни, стресс, нерациональное питание, недостаточность микроэлементов, сопутствующие заболевания и т.д.). При этом известна тесная функциональная взаимосвязь тиреоидной и репродуктивной систем, что приводит к высокой вероятности развития объединенных нарушений при расстройствах одной из этих звеньев гомеостаза. Проблема нарушений репродуктивного здоровья вызывает особенно серьезное беспокойство во всем мире и является актуальной по изучению характера влияния заболеваний щитовидной железы на беременность. Показатели заболеваемости патологиями щитовидной железы и их распространенности отличаются в разных регионах страны в зависимости от влияния факторов внешней среды и их комбинации, одним из таких является дефицит йода. Увеличение количества мертворожденных младенцев, преждевременное прерывание беременности, бесплодие, тугоухость и косоглазие новорожденных, задержка физического, полового и интеллектуального развития детей, рост показателей сердечно-сосудистых заболеваний — далеко не полный перечень негативного влияния йодного дефицита на человека. Наиболее частыми последствиями йодного дефицита у беременных является субклинический гипотиреоз. Субклинический гипотиреоз ассоциируется со многими неблагоприятными событиями во время беременности и неонатальными последствиями. Изучение особенностей течения субклинического гипотиреоза у беременных в йододефицитном регионе на сегодня остается актуальной проблемой. В статье представлен анализ публикаций баз данных PubMed, Medline за последние десятилетия.

Ключевые слова: субклинический гипотиреоз; йодный дефицит; лечение