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SUBCLINICAL HYPOTHYROIDISM AND PREGNANCY

Abstract

A special approach to the diagnosis and treatment of thyroid diseases during pregnancy is dictated by physiological characteristics and the importance of maintaining euthyroidism, especially in the first trimester of pregnancy. Despite numerous studies, to date, not all issues of diagnosis and treatment of subclinical hypothyroidism during pregnancy have been resolved. The use of uniform trimester-specific norms of thyroid-stimulating hormone (TSH) is not rational, because it leads to a very high prevalence of subclinical hypothyroidism in some populations. Therefore, it has recently been shown that it is preferable to use local TSH norms for the diagnosis of this disease. The review presents the latest data on the impact of subclinical hypothyroidism on the course of pregnancy and its outcomes. It depends on the degree of increase in TSH, as well as on the presence of an increased titer of antithyroid antibodies. TSH levels >2.5 mU/L affect pregnancy, so treatment may be beneficial, especially in women with elevated antibody titers. At the stage of pregnancy planning, at the moment, the use of general population TSH norms is justified. Treatment with a TSH level>2.5 mU/l, especially in preparation for the use of assisted reproductive technologies, is not justified.

Keywords: *subclinical hypothyroidism, pregnancy, pregnancy outcomes, pregnancy planning, fertility, reproductive technologies, TSH*

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Subklinik hipotiroidizm və hamiləlik

Xülasə

Hamiləlik dövründə tiroid xəstəliklərinin diaqnozu və müalicəsinə xüsusi yanaşma fizioloji xüsusiyyətlər öz vacibliyini qoruyub saxlayır. Çoxsaylı araşdırmalara baxmayaraq, bu günə qədər hamiləlik dövründə subklinik hipotiroidizmin diaqnozu və müalicəsinin bütün məsələləri tam həll edilməmişdir. Tiroid stimullaşdırıcı hormonun (TSH) vahid trimestr üçün xüsusi normalarının istifadəsi rasional deyildir, çünki bu, bəzi populyasiyalarda subklinik hipotiroidizmin çox yüksək yayılmasına səbəb olur. Buna görə də bu xəstəliyin diaqnostikası üçün yerli TSH normalarından istifadə etmək daha məqsədəuyğundur. İcmal subklinik hipotiroidizmin hamiləliyin gedişinə və onun nəticələrinə təsiri ilə bağlı ən son məlumatları təqdim edirik. Bu, TSH-nin artması dərəcəsindən, həmçinin antitiroid antikorlarının artan titrinin mövcudluğundan asılıdır. TSH səviyyəsi >2,5 mU/L hamiləliyə təsir edir, buna görə də müalicə xüsusilə antikor titrləri yüksəlmiş qadınlarda faydalı ola bilər.

Açar sözlər: *subklinik hipotiroidizm, hamiləlik, hamiləliyin nəticələri, hamiləliyin planlaşdırılması, məhsuldarlıq, reproduktiv texnologiyalar, TSH*

Introduction

The special attitude to subclinical hypothyroidism is explained by the fact that so far no unambiguous tactics have been developed in relation to this disease, especially when it is detected during planning or after the onset of pregnancy. Many questions are either not studied or have conflicting data, so the doctor makes a decision based on his ideas about this disease. Recently published data from numerous studies, meta-analyzes on this topic. In this regard, it seems relevant to consider some issues related to subclinical hypothyroidism and pregnancy, which are primarily of interest to the practitioner. The key issues are, firstly, the criteria for diagnosing subclinical hypothyroidism during pregnancy, which are inextricably linked with the concept of normal thyroid-stimulating hormone (TSH) for pregnant women; secondly, the impact of subclinical hypothyroidism on a woman's fertility, the course and outcomes of pregnancy.

First of all, let's discuss the concept of TSH norm for pregnant women. Differences from the general population are due to physiological changes in thyroid function during pregnancy.

The penetration of thyroid hormones through the placenta to the fetus, an increase in the concentration of thyroid-binding globulin, accompanied by increased binding of hormones, and their increased breakdown in the placenta under the influence of type 3 deiodinase dictate an increase in the synthesis of thyroid hormones in a woman's body. For enhanced synthesis of hormones, it is necessary that the thyroid gland has sufficient functional reserves and there is no iodine deficiency. An additional stimulus for increasing the functional activity of the thyroid gland in the first trimester of pregnancy is the placental hormone − human chorionic gonadotropin (hCG), a TSH agonist that can interact with its receptors. Around the 8th week, at the peak of hCG secretion, the synthesis of thyroid hormones increases, which, by a negative feedback mechanism, suppress the production of TSH, so for the first trimester, a decrease in TSH is typical, sometimes below normal. At the end of the first trimester, as hCG decreases, the TSH level is restored to its original values (Dreval, Shestakova, Nechaeva, 2007).

Studies have shown that the level of TSH and free T4, but not free T3, changes statistically significantly at different stages of pregnancy, with the minimum level of TSH observed at the beginning of pregnancy, and the minimum level of free T4 at the end of pregnancy (Bocos-Terraz, Izquierdo-Alvarez, Bancalero-Flores, 2009).

A normal level of thyroid hormones is important for both the pregnant woman and the fetus, especially in the first trimester, when the fetus's own thyroid gland is not yet functioning. Taking into account the physiological changes in thyroid function during pregnancy and the importance of maintaining a normal level of thyroid hormones for the proper formation and growth of the fetus, it is necessary to clearly define the concept of the norm for a pregnant woman, and maintain this norm throughout pregnancy. In addition, it is necessary to assess the justification for medical

interventions during pregnancy, taking into account not only the health of the woman, but also the health of her unborn child.

Since 2011, in our country, as in many other countries, trimester-specific TSH standards recommended by the American Thyroid Association (ATA) have been used: for the first trimester 0.1-2.5 mU/l, for the second trimester − 0.2-3.0 mU/l and for the III trimester − 0.3-3.0 mU/l. It should be noted that in the ATA recommendations, these standards were proposed only for laboratories that, for whatever reason, do not have their own established standards. The recommended TSH reference intervals were based on the results of six cohort studies conducted in the United States and some European countries, which showed that in the first trimester the level of TSH in pregnant women is significantly lower than in the second and third trimesters (Stagrano-Green, Abalovich, Alexander, 2011: 1086-1088).

However, the use of such a norm has led in many countries to a very high prevalence of subclinical hypothyroidism. Thus, when using TSH for the first trimester as the upper limit of the norm of 2.5 mU / l in one study conducted in China, subclinical hypothyroidism was detected in 27.8% of pregnant women, in some areas of Spain in 37%, and in the Czech Republic in 21% (Li, Shan, Mao, 2014: 99).

In this regard, in many countries of Asia and Europe, studies were conducted to determine their own TSH standards. When summarizing the data of these studies, it was shown that the level of TSH in pregnant women without thyroid pathology living in different regions differs significantly. In the first trimester, the upper limit of normal TSH values is in the range from 2.15 to 4.68 mU/l. When using regional norms of TSH, the frequency of hypothyroidism significantly decreased and averaged about 4% (Castillo Lara, Vilar Sanchez, Canavate Solano, 2017: 438).

It should be noted that higher than 2.5-3.0 mU/l, the upper limit of normal TSH was found not only in Asian countries, such as India, South Korea, China (Moon, Chung, Park, 2015: 198-204), but also in some countries Europe, for example, the Netherlands, Czech Republic, Spain (Medici, Korevaar, Visser, 2015: 704-713). These differences can be explained by ethnic characteristics, as well as the availability of iodine in the region in which the study is conducted, and the prevalence of antithyroid antibodies (La'ulu, Roberts, 2011: 913-915).

Given the accumulated data, the ATA recommendations came out in 2017 with some changes. It is still preferable to use the TSH norm for pregnant women, determined in this population, taking into account the place of residence. But if such norms cannot be determined for any reason, then it is recommended to use the reference values usually used in this population (Alexander, Pearce, Brent, 2016). However, in this case, physiological changes in TSH are not taken into account, especially in the first trimester of pregnancy. A study conducted in the Netherlands showed that when using general population norms of TSH, it is impossible to identify in time all pregnant women with reduced thyroid function, which affects pregnancy outcomes (La'ulu, Roberts, 2011: 913-915). In this regard, it is advisable to reduce the commonly used upper limit of normal TSH by 0.5 mU/l, which is also taken into account in the latest ATA recommendation.

Thus, taking into account the accumulated data and the latest ATA recommendations, it is currently recommended to use either the norms for pregnant women defined in this ethnic group, taking into account the region of residence, or the commonly used population norms with a lower upper limit of 0.5 mU/L.

Unfortunately, in Russia there are currently no national clinical guidelines for the diagnosis and treatment of thyroid diseases during pregnancy. In such a situation, each doctor is based on the information resources available to him. According to the well-known in Russia and very popular among doctors Internet resource "Tironet.ru", in clinical recommendations based on the previous version of the ATA recommendations, the level of TSH<2.5 mU/l is recommended as a goal for the treatment of overt hypothyroidism detected before pregnancy. or during it. But in the table "Thyroid diseases during pregnancy", the TSH level of 2-4 mU/l in combination with an increased titer of antithyroid antibodies is already considered as a diagnostic criterion for subclinical hypothyroidism and an indication for substitution therapy (Benhadi, Wiersinga, Reitsma, 2009: 985-991). Given the

data accumulated to date on the effect of ethnicity on TSH, the provision of the region with iodine, it can be assumed that the normal level of TSH during pregnancy will vary in different parts of our country. Therefore, it is necessary to determine the normal values of TSH in pregnant women in different regions and different ethnic groups. But so far, such studies have not been conducted in Russia, and the doctor makes his own decision.

In order to determine the indications for the treatment of subclinical hypothyroidism, it is necessary to take into account the influence of different levels of TSH on the course of pregnancy and its outcomes. Unfortunately, not all studies distinguish groups of pregnant women with varying degrees of TSH elevation and take into account the titer of antithyroid antibodies, which also affect the course of pregnancy. The study by N. Benhadi (Negro, Schwartz, Gismondi, 2010: 44-48) revealed a positive correlation between the level of TSH, starting from normal levels, and spontaneous abortion: with each doubling of TSH, the probability of miscarriage increased by 80%. An increase in TSH in the range of 2.5-5.0 mU/l in women without antithyroid antibodies is accompanied by an approximately 2-fold increase in the risk of miscarriage, both in early and late pregnancy (Zhang, Wang, Pan, 2017).

It should be noted that the effect of subclinical hypothyroidism on pregnancy increases when local TSH norms are used. An Australian study showed that the risk of miscarriage increased 3.66-fold with TSH>95 percentile in early pregnancy, although TSH>95 percentile combines subclinical and overt hypothyroidism, which may affect the results of the study (Schneuer, Nassar, Tasevski, 2012).

The risks of miscarriage increase with a combination of elevated TSH and a high titer of antibodies to thyroperoxidase (TPO). In a study by C. Lopez-Tinoco et al. (Lopez-Tinoco, Rodriguez-Mengual, Lara-Barea, 2017) demonstrated that the presence of antibodies to TPO in pregnant women with subclinical hypothyroidism increases the risk of abortion by more than 10 times.

Similar data was obtained by researchers from China. The highest risk of miscarriage was found in the group of pregnant women with subclinical hypothyroidism (TSH 5-10 mU/l) and elevated anti-TPO antibody titer (odds ratio (OR) 9.56; $p<0.001$). In a study by Y. Zhang (Zhang, Wang, Pan, 2017), the risk of miscarriage at less than 20 weeks. pregnancy increased by 2.47 times with elevated TSH>2.5 mU/l and a high titer of antithyroid antibodies.

However, not all studies have confirmed the negative impact of TSH> 2.5 mU / l on the course of pregnancy.

A Cochrane review compared pregnancy outcomes between total screening for thyroid dysfunction and screening based on risk factors. When TSH>2.5 mU/l, replacement therapy with levothyroxine was carried out in pregnant women. In the universal screening group, hypothyroidism was detected much more often (OR 3.15) and pharmacotherapy was prescribed more often, but despite the better detection of hypothyroidism in the total screening group, no differences were found in pregnancy complications and its outcomes. The authors concluded that total screening does not improve pregnancy outcomes . However, the influence of weight cannot be excluded in this study, since healthy pregnant women significantly outnumbered patients with hypothyroidism in both groups.

Conclusion

Thus, at present, the positive effect of replacement therapy with levothyroxine sodium at a TSH level of 2.5-4.0 mU/l, especially with a normal level of antithyroid antibodies, has not been proven. However, with a more pronounced increase in TSH, the positive effect of treatment is beyond doubt. Perhaps a positive effect is manifested only when using local TSH norms, which increases the importance of their determination.

Based on the latest data, it can be concluded that during pregnancy, it is better to use local TSH norms to make a decision on the appointment of treatment with levothyroxine sodium. In the absence of local norms, or with TSH> 2.5 mU/l in pregnant women with antithyroid antibodies, or

TSH> 3.5 mU / l in women without antibodies, the appointment of replacement therapy at least reduces the likelihood of spontaneous abortion, and possibly has other positive effects, especially if initiated early in pregnancy.

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