Subclinical Hypothyroidism and its Influence on Fertility and Outcome of Pregnancy

Introduction. First of all, it should be noted that there is a high risk of developing congenital hypothyroidism in a child. Your baby may also have an increased risk of abnormal thyroid development. The child is very susceptible to iodine deficiency diseases. On the part of a woman, there may be complications such as missed pregnancy, premature termination of pregnancy (miscarriage), complications in childbirth (bleeding).

To determine the indications for the treatment of subclinical hypothyroidism, it is necessary to take into account the effect of different levels of TSH on the course of pregnancy and its outcomes. Unfortunately, not all studies identify 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. In a study by N. Benhadi [1,3], a positive correlation was found between the TSH level, starting from normal values, 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 [9]. It should be noted that the effect of subclinical hypothyroidism on gestation increases with the use of local TSH norms. A study in Australia showed that the risk of miscarriage increased 3.66-fold with TSH> 95th percentile in early pregnancy, although TSH> 95th percentile combines subclinical and overt hypothyroidism, which may affect the study results [6]. The risk of spontaneous abortion increases with a combination of elevated TSH and high titer of antibodies to thyroid peroxidase (TPO). In a study by C. Lopez-Tinoco et al. [2] demonstrated that the presence of subclinical hypothyroidism during pregnancy is fraught with a particular danger, since it does not manifest itself, and, therefore, the consequences can be most severe. Hypothyroidism is an underactive thyroid gland. Subclinical hypothyroidism is characterized by the absence of symptoms, however, tests signal an increase in TSH (thyroid stimulating hormone of the pituitary gland - it is he who is responsible for regulating the secretion of thyroid hormones). Therefore, it is very important to take all the tests prescribed by the doctor on time, because timely and correct treatment can prevent the consequences of hypothyroidism. It is women who are most susceptible to the appearance of subclinical hypothyroidism. In this abstract we give a noticable information for all doctors about this case and it’s consequences.

Keywords: Subclinical hypothyroidism, thyroid stimulating hormone, pregnancy, miscarriage.
of antibodies to TPO in pregnant women with subclinical hypothyroidism increases the risk of abortion by more than 10 times. Researchers from China received similar data. The highest risk of miscarriage was found in the group of pregnant women with subclinical hypothyroidism (TSH 5–10 mU / L) and an increased titer of antibodies to TPO (odds ratio (OR) 9.56; p <0.001).

In a study by Y. Zhang [1,9], the risk of miscarriage in less than 20 weeks pregnancy increased by 2.47 times with an elevated TSH> 2.5 mU / L and a high titer of antithyroid antibodies. However, not all studies have confirmed the negative effect of TSH> 2.5 mU / L on the course of pregnancy. Thus, in the study by H. Liu [2], statistically significant differences in the frequency of abortion in the groups of pregnant women with TSH <2.5 mU / L and TSH in the range of 2.5–5.22 mU / L were not revealed, although there was no tendency to increase was observed in the group with increased TSH (3.3% versus 2.2%, p = 0.083).

A Cochrane review compared pregnancy outcomes for total thyroid dysfunction screening versus screening based on risk factors. With TSH> 2.5 mU / L, pregnant women underwent replacement therapy with levothyroxine. 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, there were no differences in pregnancy complications and outcomes. The authors concluded that total screening does not improve pregnancy outcomes [2,3]. However, the influence of mass cannot be excluded in this study, since healthy pregnant women significantly outnumbered patients with hypothyroidism in both groups.

Conflicting data were obtained in the study of the association of subclinical hypothyroidism and preterm birth. In a study by Casey et al. [4] revealed a connection between subclinical hypothyroidism and childbirth earlier than 34 weeks gestation, but such a relationship was not found for periods of less than 32 or less than 36 weeks. Subsequently, in such studies, conflicting data were obtained, due in part to the unification of pregnant women with subclinical and overt hypothyroidism into one group, as well as the inclusion of pregnant women with antithyroid antibodies in the study.

As shown by T. Korevaar et al. [5], the complicated course of pregnancy depends on the degree of TSH increase. Pregnant women were divided into groups depending on the TSH level: 2.5-4.0 mU / L or more than 4.0 mU / L. With TSH below 4.0 mU / L, there was no increase in the incidence of preterm birth, while with TSH> 4.0 mU / L, the risk of childbirth earlier than 37 weeks increased 1.9 times, and previously 34 weeks - 2.5 times. But the primary analysis was carried out without taking into account the titer of antibodies to TPO. When pregnant women with elevated antibodies to TPO were excluded from the analysis, the difference between the groups disappeared, and even an isolated increase in TSH> 4 mU / L did not affect the rate of preterm birth. This study has once again demonstrated the importance of distinguishing between pregnant women with normal and elevated titer of antibodies to TPO, since they are an independent risk factor for complicated pregnancy.

The effect of subclinical hypothyroidism on the development of pregnancy-associated hypertension and preeclampsia seems to be dubious. Previously, cohort studies have identified an association between subclinical hypothyroidism and preeclampsia, but only if screening for hypothyroidism was performed late in pregnancy. If the function of the thyroid gland was studied up to 20 weeks pregnancy, no dependence was found [6,7]. It is assumed that at the initial stages of development of preeclampsia, the placenta can produce factors that affect the function of the thyroid gland [8]. With an increased TSH (> 2.15 mU / l) in the first trimester of pregnancy, there was no increase in the frequency of pregnancy complications, including preeclampsia, developing after 20 weeks. [nine]. When studying moderately elevated TSH, from 2.5 mU / L to 97.5 percentile, and the population norm, an increase in the incidence of preeclampsia was found only in pregnant women with high normal free T4, in the rest the high normal TSH level did not affect the frequency of preeclampsia [1]. However, some studies still found an association between elevated TSH and high blood pressure.
during pregnancy. For example, the study by L. M. Chen [10] revealed an increased risk of gestational hypertension, as well as low fetal weight in pregnant women with subclinical hypothyroidism. That is, at first glance, diametrically opposite results were obtained. But in this study, subclinical hypothyroidism was diagnosed with TSH> 3.47 mU / L, which was defined as the upper limit of the norm in this laboratory, which is significantly higher than 2.5 mU / L. Probably, it is the TSH level used to diagnose subclinical hypothyroidism that affects the results of studies of its effect on pregnancy.

Usually, in case of conflicting data, a meta-analysis method is used to reveal the truth. A recent meta-analysis of 18 cohort studies showed that subclinical hypothyroidism is associated with several adverse pregnancy outcomes, such as miscarriage (OR 2.01; 95% confidence interval (CI) 1.6–2.44), placental insufficiency (OR 2.14 ; 95% CI 1.23–3.7) and increased neonatal mortality (OR 2.58; 95% CI 1.41–4.73). There was no association with other adverse outcomes such as preeclampsia [1]. It should be noted that the studies included in the meta-analysis used different TSH cut-off values for the diagnosis of subclinical hypothyroidism. Only in 6 out of 18 studies the TSH threshold was the level of 2.15–2.5 mU / L. Moreover, three studies included pregnant women with TSH ≥2.5 mU / L and a normal level of free T4. That is, the degree of TSH increase could be different, from 2.5 to 10 mU / L. And as we can see from other studies, different degrees of TSH elevation have different effects on pregnancy outcomes. In most meta-analysis studies, subclinical hypothyroidism was diagnosed with TSH> 3.5 mU / L. And this is precisely the upper limit of the TSH norm for pregnant women recommended today, if you use the modified general population norms. The influence of TSH from 2.5 to 4 mU / l on the neuropsychiatric development of the fetus and other indicators of fetal health has not been identified [1,2]. Given the currently obtained data, it can be assumed that TSH> 2.5 mU / L is associated with spontaneous abortion. Other adverse pregnancy outcomes are associated with a higher TSH threshold. Pregnant women with elevated TSH and antithyroid antibodies deserve special attention. In this case, the adverse effect on the course of pregnancy increases. But it is necessary to understand whether the situation will change for the better if the function of the thyroid gland is compensated for in subclinical hypothyroidism in pregnant women. Many researchers support the idea of treatment, because it is quite safe and can have a positive effect on pregnancy [3]. Pregnancy outcomes did not differ in women taking levothyroxine sodium for overt or subclinical (TSH> 2.5 mU / L) hypothyroidism and in euthyroid women. And this indicates the safety of treatment with sodium levothyroxine, at least in relation to pregnancy.

The administration of levothyroxine sodium to pregnant women with TSH above the norm determined in the local laboratory led to an overall decrease in pregnancy complications. Moreover, the effect depended on the timing of the start of treatment and the time spent on reaching the target TSH level. The complication rate decreased if treatment was started before 12 weeks. pregnancy and the goal of treatment was achieved in less than 4 weeks. [1]. In a study by S. Maraka et al. [13] showed that the appointment of substitution therapy for TSH 2.5–5 mU / L reduces the risk of intrauterine growth retardation and a low score for the state of the fetus at birth according to the Apgar scale. There were no differences in other pregnancy outcomes, including spontaneous abortion.

In other studies, the positive effect of treatment with levothyroxine was detected only in groups of pregnant women with TSH> 4.0–5.0 mU / L. At the same time, one study showed a significant decrease in the incidence of preterm birth (OR 0.38; 95% CI 0.15–0.98). In pregnant women with TSH 2.5–4.0 mU / L, the appointment of substitution therapy did not improve pregnancy outcomes [6,8]. Thus, at present, the positive effect of replacement therapy with sodium levothyroxine at a TSH level of 2.5–4.0 mU / L, especially at a normal level of antithyroid antibodies, has not been proven. At the same time, with a more pronounced increase in TSH, the positive effect of treatment is beyond doubt. It is possible that a positive effect is manifested only when using local TSH rates, 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 rates to decide 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 substitution therapy at least reduces the likelihood of spontaneous abortion, and possibly has both other positive effects, especially if initiated early in pregnancy.

An important question is what is the effect of subclinical hypothyroidism on a woman's fertility. And this question gives rise to two more: 1) at what level of TSH is it necessary to start treatment when planning pregnancy and what is the target level of TSH at the stage of planning pregnancy. When a woman is identified at the stage of planning pregnancy, TSH is more common the norm, the appointment of treatment is not in doubt. It is more difficult to decide whether to need treatment with a normally high level of TSH. Recently, there is more and more data on the effect of moderately elevated TSH on fertility. Indeed, it was found that with infertility in a woman, the level of TSH is higher than in the control group, especially if the cause of infertility was ovarian dysfunction or the cause was unknown [12]. In one of the studies, the administration of levothyroxine sodium to infertile women with TSH > 3 mU/l in 84.1% of women was accompanied by pregnancy, and in some women it was spontaneous [4]. However, earlier studies did not reveal an association of increased TSH and decreased fertility in women [1]. The revealed single-time elevated TSH level > 2.5 mU/L at the stage of pregnancy planning can independently decrease after the onset of pregnancy. In one small study, it was shown that in 50% of pregnant women with TSH > 3 mU/L at the planning stage after pregnancy, the TSH level independently normalized and became less than 2.5 mU/L. Unfortunately, this study did not investigate the differences between groups with elevated and normal post-pregnancy TSH levels [10].

A larger study of 482 women who underwent in vitro fertilization (IVF) assessed the likelihood of pregnancy and continued pregnancy based on baseline TSH. In 55% of pregnant women, after the onset of pregnancy, TSH decreased from the initial level of 2.5–4.0 mU/L to 2.5 mU/L. The onset of pregnancy did not depend on the baseline TSH level. The authors concluded that treatment with an increase in TSH from 2.5 to 4.0 mU/L can be postponed until pregnancy, when this level will be confirmed [3].

On the other hand, in a population study conducted in China, a dependence of the outcomes of spontaneous pregnancy on the TSH level, determined within 6 months, was found. before pregnancy. In women with TSH 2.5–4.28 mU/L, when compared with women with TSH below 2.5 mU/L (0.48–2.49 mU/L), a slight but still statistically significant increase in the frequency of spontaneous miscarriages (OR 1.1) and premature births (OR 1.09). More severe complications of pregnancy, such as perinatal mortality, intrauterine fetal death, and caesarean section, were observed only at TSH levels > 4.0 mU/L [11].

Many studies evaluate the effect of subclinical hypothyroidism and its treatment on outcome various assisted reproductive technologies (ART). Special attention to this group of women is explained by the use of high doses of estrogens in the stimulation process, which can manifest compensated thyroid insufficiency. There was no negative influence of the TSH level from 2.5 to 4.9 mU/L on the results of insemination. One study in euthyroid women found an inverse association between TSH levels at the time of pregnancy and the frequency of spontaneous miscarriages. In another similar study, no association was found between an increased level of antithyroid antibodies and/or TSH > 2.5 mU/L on the birth rate in women after insemination [4,6], although in a retrospective study the effectiveness of insemination increased when substitution therapy was prescribed to women with TSH levels > 2.5 mU/L [7]. IVF efficiency at a TSH level <2.5 mU/L was even higher and the quality of embryos was higher than in women with a higher TSH [12].
But not all studies have the same data. Thus, M. Aghahosseini et al. [5] did not reveal statistically significant differences in the incidence of pregnancy as a result of ART, depending on the level of TSH. In a prospective study, it was shown that the appointment of substitution therapy in women with subclinical hypothyroidism (TSH 4.2–20.0 mU / L and free T4 is normal) before IVF improves its outcomes and they are comparable to euthyroid women. But we are talking about TSH levels above the population norm, but not about high-normal TSH. After the appointment of substitution therapy, differences in pregnancy outcomes depending on the target TSH level (0.5–2.5 or 2.5–4.0 mU / L) were not obtained, only its normalization was sufficient.

Conclusion. Thus, the appointment of substitution therapy at the stage of pregnancy planning, including for women planning ART, is indicated only when the TSH level rises above the general population norm. The use of standards for pregnant women at this stage is not justified. An interesting question is also about the long-term risks of women with subclinical hypothyroidism identified during pregnancy.

1. In a study conducted in India, it was shown that 2 years after pregnancy, 17.8% of women developed subclinical or overt hypothyroidism. The risk factors for the disease were age (23.6–25.5 years), goiter, the degree of TSH increase during pregnancy (7.9–5.1 mU / L), and an increased titer of antibodies to TPO [3]. Therefore, in the presence of such risk factors, periodic testing for hypothyroidism should be carried out; termination of pregnancy, gestational diabetes, preeclampsia and premature birth.

2. The relationship of subclinical hypothyroidism and impaired fetal intellectual development is contradictory.

3. Hypothyroxinemia in a pregnant woman is associated with impaired neuropsychological development of the fetus.

List of used literature:


