Evaluation of clinical efficacy of different doses of LT4 in the treatment of pregnant women with normal-high TSH and positive TPOAb in the first half of pregnancy

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Research background and purpose

Thyroid hormone (TH) is essential for fetal brain development. The fetal thyroid develops at 8-12 weeks and matures at 18-20 weeks to function. Therefore, fetal development in the first half of pregnancy (gestational age ≤ 20 weeks) depends largely on the supply of maternal TH. Normal-high TSH value: It is a thyroid function state unique to women in the pre-pregnancy and pregnancy period; thyroid autoantibodies (mainly TPOAb) during pregnancy reflect the thyroid autoimmune state. TPOAb positivity is considered to be a mild thyroid dysfunction, which can affect placental function through inflammatory reactions such as IL-6, IL-8, IL-10 and tumor necrosis factor α, and increase the risk of adverse pregnancy outcomes such as miscarriage. The intestinal microbiota also plays a vital role in shaping and regulating the immune system and immune response. Our research group studied the biological characteristics of the intestinal flora in patients with hypothyroidism during pregnancy and abnormal TPOAb and found that abnormal TPOAb was associated with intestinal flora.

Normal-high TSH with positive TPOAb is associated with adverse pregnancy outcomes such as miscarriage, premature birth, premature rupture of membranes, preeclampsia, placental abruption, and fetal growth restriction. Taking levothyroxine (LT4) can reverse the harmful effects of TPOAb and TGAb levels, improve patients' thyroid function, and reduce the incidence of adverse pregnancy outcomes such as gestational diabetes, premature rupture of membranes, miscarriage, premature birth, and macrosomia. The "Guidelines for the Prevention and Management of Thyroid Diseases During Pregnancy and Childbirth" pointed out that in early pregnancy, when TSH is between 2.5mIU/L and the upper limit of the pregnancy reference value (or 4.0mIU/L in early pregnancy) with positive TPOAb, 25ug-50ug LT4 should be given for treatment. However, high-dose LT4 may have adverse reactions such as palpitations, insomnia, sweating, and nausea. Therefore, this study explored the differences in clinical efficacy of different doses of LT4 in the treatment of pregnant women with normal-high TSH and positive TPOAb.

Research plan

1. Research content

Pregnant women diagnosed with normal-high TSH and positive TPOAb before 20 weeks of pregnancy who received perinatal care and gave birth in the Third Affiliated Hospital of Zhengzhou University from July 2019 to October 2023 were selected and divided into two groups, A and B, with 100 cases in each group according to the dose of LT4 of 25ug and 50ug; those who did not take LT4 were group C, with 200 cases. The clinical efficacy of different doses of LT4 in the treatment of pregnant women with normal-high TSH and positive TPOAb in the first half of pregnancy was explored.

Inclusion criteria: (1) Diagnosed with normal-high l TSH and positive TPOAb before 20 weeks of pregnancy (TSH: 2.5mIU/L-upper limit of reference range, TPOAb > 34IU/mL), FT4 in the normal range (FT4: 12-22pmol/L) in line with the diagnostic criteria established by the Laboratory Department of the Third Affiliated Hospital of Zhengzhou University; (2) All subjects voluntarily participated and signed informed consent

Exclusion criteria: (1) Multiple pregnancy (2) Assisted reproductive technology; (3) Suffering from

serious diseases or diseases that affect pregnancy outcomes, such as dysfunction of important organs; (4) Suffering from thyroid disease; (5) Diagnosed with a history of other endocrine, antiphospholipid syndrome and other autoimmune diseases; (6) Taking drugs that affect the thyroid gland (7) LT4 allergy

2. Research steps

① Select pregnant women who meet the inclusion and exclusion criteria and group them, and record the basic information of the pregnant women, mainly including: age, height, weight, pregnancy and delivery history, thyroid function and other serological indicators.

②Collect blood and stool samples from pregnant women in groups A and B before and after LT4 treatment, track thyroid function indicators such as TSH, FT4, TPOAb before and after treatment in the three groups of pregnant women, and record maternal and fetal nutritional development.

③Pregnancy outcomes: Track and follow up maternal and fetal outcomes, including the incidence and mode of delivery of adverse pregnancy outcomes such as miscarriage, premature birth, gestational hypertension, gestational diabetes, premature rupture of membranes, fetal growth restriction, macrosomia, intrapartum blood loss, neonatal sex, weight, head circumference, height, Apgar score, thyroid disease, etc.

④Statistical methods: SPSS 26.0 software was used for statistical analysis; continuous data were described by (mean ± standard deviation), and count data were expressed by frequency and rate; two independent samples that met normal distribution and homogeneity of variance were analyzed by t test and corrected t test; comparison of binary data between two independent samples of count data was analyzed by X2 test and corrected X2 test; $P < 0.05$ was considered statistically significant.

Safety Analysis

Levothyroxine is a common drug for the treatment of thyroid diseases and has been proven to be safe and effective. The "Guidelines for the Prevention and Treatment of Thyroid Diseases during Pregnancy and Childbirth" recommends that 25ug-50ug levothyroxine (LT4) be given for treatment when TSH in early pregnancy is between 2.5mIU/L and the upper limit of the pregnancy reference value (or 4.0mIU/L in early pregnancy) with positive TPOAb. This study collected feces and a small amount of peripheral blood from patients, which will not have adverse effects on the subjects.

Feasibility Analysis

Levothyroxine is an effective drug for the treatment of thyroid diseases. It is easily absorbed by the body, has a high utilization rate, and is widely used in clinical practice. The information on the condition of the subjects collected in this study is obtained from routine perinatal care and will not harm their health and rights; the peripheral blood collection in this study is often carried out at the same time as other similar blood test items, without the need for additional blood collection, and the amount of blood collected is small, which causes little harm to the research subjects, and the rest of the samples are collected non-invasively.

Result

(1) There was no significant difference between the disease group and the control group in general conditions such as age, BMI, gestational age, etc.; (2) The disease group had higher TC and LDL levels than the control group, as well as high-sensitivity C-reactive protein (hsCRP) levels, Th17, Th17/Treg ratio was significantly higher than that of the control group, and the percentages of Treg and IL-10 were significantly lower than the control group; (3) TSH, hsCRP, Th17, Th17/Treg ratio, and TNF-α in the disease group after LT4 intervention were significantly higher decreased, and FT4, Treg, and IL-10 increased significantly; (4) The incidence of SIBO in the disease group was higher than that in the control group, and the incidence of SIBO in the disease group after intervention was lower than before intervention; (5) Compared with the HA group, The TSH level of the HB group was lower and the IL-10 level was higher, but there was no significant difference in the levels of blood lipids such as TC, TG, HDL, LDL and other inflammatory factors such as hsCRP and IL-2 between the two groups; (6) Correlation analysis in pregnant women with normal-high TSH values and positive TPOAb: TSH is positively correlated with hsCRP, negatively correlated with Treg proportion, TPOAb is positively correlated with TNF-α; IL-10 levels are negatively correlated with IL-2 and IL-4 levels; TC is positively correlated with hsCRP.