



## The adverse effects of hypothyroidism and hyperthyroidism during pregnancy

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### ABSTRACT

Due to the important role of thyroid disorders on reproductive health of the women of childbearing age, pregnancy outcome, fetal health, and neurodevelopment of the infant, providing comprehensive assessment of the treatments used for preventing hyperthyroidism and hypothyroidism seems to be essential. Therefore, evaluating the efficacy of different treatments of the thyroid disorders would be beneficial in better managing and controlling the disease during pregnancy. Hypothyroidism (a deficiency of thyroid hormone) is a common thyroid disorder, which might increase the incidence rate of miscarriage, pre-eclampsia, placental abruption, and preterm delivery. Hyperthyroidism, which is not a common disorder during the pregnancy not only leads to similar adverse effects as hypothyroidism but also can result in stillbirth and intrauterine growth restriction. Levothyroxine is the preferred treatment of hypothyroidism and the only drug therapy recommended for treating hyperthyroidism during pregnancy. In this study, we aimed to briefly review the adverse effects of hyperthyroidism and hypothyroidism during pregnancy and review the effects of recent suggested treatments for controlling thyroid disorders on pregnancy outcomes.

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## Introduction

### Thyroid hormones

The concentration of the thyroid hormone can affect the heart, connective tissue, metabolite rate, glucose metabolism, protein catabolism, cholesterol level, etc. These hormones can also affect the growth and development; specifically the development of the cortex and ganglia of the brain. Iodine obtained from the diet is utilized by thyroid gland for producing thyroid hormones including thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>) and the rest is excreted in the urine. The thyroid hormone production is controlled by the thyrotropin (thyroid-stimulating hormone, TSH) secreted from pituitary, which is regulated by hypothalamus through generating thyrotropin-releasing hormone (TRH) (1). Thyroid hormones are

among the essential hormones for the normal metabolism, growth, development, and maturation. Major part of serum transporting of the endogenous T<sub>3</sub> and T<sub>4</sub> is done by binding to the thyroxine-binding globulin, transthyretin and albumin. During pregnancy, the increase of serum concentration of these binding proteins leads to the rise of the T<sub>4</sub> concentration rate. Thyroid physiology would be altered during pregnancy due to hormonal changes. After a few weeks, the thyroid-binding globulin (TBG) will increase and reach to 2-3 fold higher concentration than its pre-pregnancy levels. The concentration of T<sub>4</sub> and T<sub>3</sub> would increase especially between 6 and 12 weeks of pregnancy as the consequences of TBG rise (2).

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## Literature review

### Thyroid diseases

Pregnancy is among the possible risk factors of the thyroid dysfunction. Normal thyroid function is essential for continuing normal reproduction. Hormonal changes such as increase in the estrogen level during pregnancy might lead to the significant changes of the thyroid function and iodine metabolism that eventually lead to higher obstetric complications in some cases (3).

In some pregnancy cases, normal physiological changes of the thyroid and nonspecific symptoms during congestion can inhibit thyroid disorder detection.

The prevalence of the thyroid dysfunction during pregnancy is estimated to be higher in regions with severe iodine deficiency compared with iodine-sufficient areas, which necessitates the thyroid function controlling in all the pregnant women to identify the cases with thyroid disorders (4). The prevalence of thyroid dysfunctions has been estimated to be almost 5% of all the pregnant women and 5-10% among the women at childbearing age.

Thyroid diseases as the second most common disorder after the diabetes mellitus comprise hyperthyroidism, hypothyroidism, chronic autoimmune thyroiditis, and hypothyroxinemia.

Habitual abortion, preterm labor, fetal death, retardation, congenital malformations, bleeding and depression after birth, anemia, cardiac disorder, and increased risk of maternal morbidity and mortality are various consequences of thyroid dysfunction during pregnancy (5,6).

### Hyperthyroidism

Hyperthyroidism can be defined as the overproduction of the thyroid hormones (T<sub>4</sub> or T<sub>3</sub>) with the prevalence rate of approximately 1% to 4% in the general population. It represents with a wide variety of the symptoms, which are different between patients such as anxiousness, tachycardia, atrial fibrillation, increased heat sensitivity, perspiration, skin changes, loss of weight, insulin resistance, fatigue, and shivering. The major cause of the hyperthyroidism, almost in 85% of the cases, is proposed to be the autoimmune Graves disease, which might be diagnosed through symptoms such as heat intolerance, enlargement of thyroid gland, increased T<sub>4</sub>, presence of thyroid autoantibodies, fetal tachycardia and cardiac failure, and fetal retardation (7). Graves disease has higher prevalence in women than men; specifically in women at reproductive age (20 to 40 years old) (8). Thyroid toxic adenoma, toxic nodular goiter, thyroid inflammation, gestational trophoblastic disease, struma ovarii and thyrotropin receptor (TSHR) activation are

other possible conditions, which might lead to the occurrence of hyperthyroidism (9-11).

Radioactive iodine uptake (RAIU) test is a diagnostic method of thyroid disorders especially hyperthyroidism, which is not appropriate to be used during pregnancy. Increased risk of several complications such as congestive heart failure, thyroid crisis, placental abruption, pre-eclampsia, miscarriage, stillbirth, premature birth, and intrauterine growth restriction (IUGR) has been illustrated as the consequences of hyperthyroidism during pregnancy. In order to treat the thyroid diseases of pregnant mother and prevent the incidence of the further complications, diagnosis and controlling of the thyroid status of the pregnant mother and the fetus is important early in the pregnancy.

Although radioactive iodine (radioiodine) therapy, antithyroid medications, and surgery are different types of hyperthyroidism treatment, only pharmacotherapy is suggested to be appropriate for the pregnant women. By performing radioiodine therapy, the maternal hyperthyroidism would be treated as a result of destroyed thyroid glands, which can lead to the neonatal hypothyroidism (12).

Thionamides, propylthiouracil (PTU), methimazole and carbimazole are different medications that can be used for treating the hyperthyroidism. Thionamides and methimazole act by blocking the enzyme thyroperoxidase, which leads to the inhibition of thyroid hormone synthesis in thyroid gland (8). Various side effects have been identified by using hyperthyroidism-treating drugs during pregnancy. Pruritus, rash, hives, swelling, fever, nausea, vomiting, granulopenia, septicemia, vasculitis, and liver dysfunction have been mentioned as the adverse effects of pharmacotherapy for treating hyperthyroidism (8).

In pregnancies with hyperthyroidism incidence, methimazole and thionamides are proposed drugs, which might lead to fetal birth abnormalities and maternal liver injuries, respectively (13).

Although the lower doses of methimazole control hyperthyroidism better and lead to lower toxicity in comparison to thionamides, pregnancy is the exception condition for using methimazole. Application of methimazole might lead to some neonatal undesirable outcomes with low prevalence including aplasia cutis (scalp lesions), choanal atresia (blocked nasal passage), and oesophageal atresia. Although thionamides may cause maternal liver injury and hepatic related complications, it is the preferred medication (a first-line agent) for managing the pregnant women hyperthyroidism specifically at the first trimester (14). Administering the antithyroid drugs has been recommended to be as low dose

as possible. Overutilization should be avoided due to the potential risks of hypothyroidism and some long-term effects in fetus.

### Hypothyroidism

Hypothyroidism (overt or subclinical types) can be observed among the pregnant women with the incidence rate of 3% to 5% of general population.

Low level of free thyroxine hormone accompanying with increased TSH is defined as overt hypothyroidism whereas normal level of thyroid hormone and high TSH can be explained as sub-clinical hypothyroidism. The situation with normal free thyroxine level and decreased TSH can be defined as isolated maternal hypothyroxinaemia. The general presentations of hypothyroidism might be increased weight, constipation, weakness, muscle cramps, cold intolerance, and dry skin. Iodine deficiency with the prevalence of 2 billion people is known as a major cause of hypothyroidism specifically in Central and South America and Asia (15). Thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) are two types of antithyroid autoantibodies that rise in concentration during pregnancy in the first trimester of almost 18% of pregnancies. These autoantibodies can lead to hypothyroidism and other consequent disorders by affecting the thyroid such as spontaneous abortion, premature birth, infertility, maternal depression, or thyroiditis after delivery (15, 16). Thyroid autoimmunity is one of the major causes of hypothyroidism. Therefore, normal functioning of the endocrine and immune system is essential for maturation of oocytes and preventing the infertility and reproductive complications.

According to several previous retrospective studies since 1993, various factors have been mentioned as consequences of undiagnosed or

untreated hypothyroidism including abortion, hypertension, anemia, placental abruption, haemorrhage after delivery, several neonatal complications, requirement of the intensive care unit, and various fetal neurodevelopmental disorders (17-20)

A considerable reduction in the incidence of fetal neurodevelopmental disorders has been reported due to an appropriate diagnosis and controlling of overt or subclinical hypothyroidism of pregnant women (21). Because of the principal effect of iodine deficiency in occurrence of hypothyroidism and consequent cretinism, application of iodized salt, bread, water, and oil as iodine supplementation might be able to control iodine deficiency-induced disorders. Increased thyroxine intake has been proposed to be beneficial during pregnancy in iodine-sufficient conditions to treat hypothyroidism. Administering selenium during pregnancy has been suggested to be influential in decreasing the possibility of hypothyroidism incidence.

Detailed information of two clinical trials, which studied the efficacy of different treatment applied for reducing the hypothyroidism rate during pregnancy, is summarized in Table 1. These trials evaluated the incidence of pre-eclampsia and preterm delivery as the primary outcomes. Changes of the gestational hypertension, serum TSH and free T4, miscarriages, abruption, and clinical characteristics of newborns were considered as secondary outcomes of these trials.

Negro et al, in 2006, compared the efficacy of different levothyroxine (LT) doses on managing the thyroid function of TPOAb-positive pregnant women, with no intervention during pregnancy. According to Negro et al, using LT for TPOAb(+) pregnant women, only resulted in significant reduction of preterm labor and did not decrease

**Table 1.** Detailed information of two randomized controlled trials about the efficacy of different interventions used for pregnancy-induced hypothyroidism.

First author Year Country Reference	Participants	Intervention	Results
Negro 2006 Italy (21)	105 TPOAb(+) patients LT** gr: 55 No treatment gr: 50	LT versus no treatment LT dose: 0.5-1 µg/kg/d (based on TSH and thyroid peroxidase antibody titers)	Preterm delivery: RR 0.28; 95% CI (-0.10 to -0.80) Pre-eclampsia: RR 0.61; 95% CI (-0.11, 3.48) Miscarriage: RR 0.25; 95% CI (-0.06, 1.15)
Negro 2007 Italy (22)	169 TPOAb(+) patients Se*** group: 77 Placebo: 74	Se versus Placebo Se dosage: 200 µg/day after 12 weeks gestation Iodized salt was used by all the patients	Preterm delivery: RR 0.96; 95% CI (-0.20 to 4.61) Pre-eclampsia: RR 1.44; 95% CI (-0.25 to 8.38) Miscarriage: RR 0.85; 95% CI (0.30 to 2.42)

\*TPOAb(+): Thyroid peroxidase antibody positive; \*\*LT: Levothyroxine; \*\*\*Se: Selenomethionine (selenium)

the incidence of preeclampsia (21). In another clinical trial by Negro et al in 2007, the efficacy of selenium (Se) supplementation on reducing pregnancy complications and postpartum thyroid dysfunction was compared for the first time with placebo. In this study, not only no significant reductions were observed in preterm labor and preeclampsia rates as primary outcomes, but also the incidence of miscarriage did not decrease significantly using Se (22). According to two mentioned studies of Negro et al, application of LT or Se would not lead to significant reduction of pre-eclampsia in TPOAb-positive pregnant women. It can be also concluded that application of LT might be able to reduce the rate of preterm labor in TPOAb-positive pregnancies unlike the application of Se.

According to the study of Negro et al in 2007, postpartum thyroid dysfunction can be decreased significantly (RR 0.59; 95% CI 0.38 to 0.90)-(RD -0.20; 95% CI -0.35 to -0.05) by using Se supplementation for TPOAb-positive pregnant women (22).

In both of the studies of Negro et al by using LT or Se, significant reduction was only observed in miscarriage rate and no significant reduction was revealed in gestational hypertension or placental abruption as the secondary outcomes.

The efficacy of pre-pregnancy LT therapy in hypothyroidism cases to reduce the gestational complications during pregnancy was also evaluated in one prospective study (23). In this study, preconception suppressive LT therapy in hypothyroidism cases was considered to be effective in thyroid function during pregnancy, which was similar to the results obtained by Negro et al in 2006 (23). Initiating the application of increased doses of LT before the 11 weeks of gestation would significantly decrease the possibility of maternal hypothyroidism and further complications (24).

In conclusion, although iodine deficiency and thyroid disorders are among the public health dilemmas, there are not adequate country-based epidemiological studies about the prevalence of thyroid dysfunction. Although LT and Se are two common treatments in women with hypothyroidism anticipating pregnancy, further trials are needed to establish the efficacy of these treatment effects on improving the pregnancy outcomes.

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## Conflict of Interest

The authors declare no conflict of interest.

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