



## HYPOTHYROIDISM AND HYPOTHYROXINEMIA IN PREGNANCY: AN OVERVIEW IN THE TIME OF CORONAVIRUS DISEASE 2019

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### ABSTRACT

In normal pregnancy, the maternal thyroid gland undergoes alterations to maintain the necessary levels of thyroid hormones (THs) in each gestational period. However, various factors may reduce TH levels, potentially impacting the onset and development of pregnancy. Such cases of thyroid dysfunction are divided into overt (clinical) hypothyroidism, subclinical hypothyroidism, or isolated hypothyroxinemia, depending on the severity of deficiency. The reported incidence of overt hypothyroidism in pregnancy is 0.3-1.9%, while that of subclinical hypothyroidism is 1.5-5% and that of isolated hypothyroxinemia ranges between 1.3%-25.4%. On a global level, the most common factor for hypothyroidism is iodine deficiency, but in regions where iodine sufficiency is the norm, the most cause is autoimmune thyroiditis or Hashimoto's thyroiditis. Early diagnosis and treatment of low TH levels can play a significant role in lowering the risk of negative outcomes such as recurring miscarriage, gestational hypertension, premature birth, and adverse fetal outcomes. However, there is no agreement on TH reference levels during pregnancy to be used to diagnose thyroid dysfunction, nor is there agreement on universal screening of pregnant women for thyroid function in the first trimester, so specific studies for different populations are needed. In extremely stressful events, as is the case during the COVID-19 pandemic, thyroid function may be altered early in pregnancy, so pregnant women in these situations merit extra monitoring of their thyroid function. As managed hypothyroidism is not a risk factor for more negative outcomes in patients with COVID-19, no extra precautions or measures need to be taken.

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### Introduction

In pregnancy, the body undergoes changes in hormones and metabolism that may cause various pathophysiologic processes, some of which can be serious if not treated. One of these is thyroid dysfunction, which causes complications in the mother and fetus [1]. Comprehensive understanding of the pathophysiology, diagnosis, and treatment of thyroid dysfunction is crucial to mitigate adverse maternal and fetal outcomes [2], but changes in hormones during pregnancy make diagnosing and managing thyroid disease more challenging.

Pregnancy puts a great deal of stress on the thyroid gland, so women with iodine deficiency or reduced thyroid reserve may develop hypothyroidism, the most widespread thyroid disorder reported in pregnancy, with subclinical hypothyroidism seen more often than overt hypothyroidism [1, 3]. However, data on the prevalence of hypothyroidism during pregnancy varies as its diagnosis depends on the upper end of the reference range and technique used to measure TSH [1]. This paper overviews this disorder in pregnancy, starting from the physiological changes and symptoms to the way it is diagnosed and treated, in addition to its prognosis. The relationship between COVID-19 and thyroid dysfunction is also addressed.

#### *Thyroid Hormones in Pregnancy*

##### *The Pregnant Woman*

The physiology of the maternal thyroid gland undergoes the following alterations to ensure that levels of THs are sufficient at each gestational stage during normal pregnancy [1, 4]:

1. THs circulate in the blood with the help of transthyretin, albumin, and TBG [4, 5]. In pregnancy, TBG levels double or triple, producing an increase in total T<sub>4</sub> and T<sub>3</sub> levels and a decrease in TSH concentration [5, 6]. The other two

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proteins—transthyretin and albumin—are released into the bloodstream to control the movement of hormones from the mother to the fetus, and play a role in how THs are reabsorbed and affected by deiodinases [4]. Transthyretin protects against the deiodination of THs in the placental tissue, thereby raising TH concentrations and facilitating their passage into the fetal circulation [4]. Albumin binds with THs with a low affinity but high capacity and has been found in the trophoblast glycocalyx, where it helps recapture and protect THs or works to transport the hormone in the fetal circulation [7].

2. The iodothyronine deiodinases play a role in the regulation of THs [8]. For instance, deiodinases can adjust the TH signaling in target cells to modulate the cytoplasmic pool of  $T_3$  and the level of  $T_3$  in the nucleus. They also affect the saturation receptors of thyroid hormones. These actions are independent of circulating THs concentrations [5]. In pregnancy, the level of deiodinases expressed in the uterus is altered, with type III deiodinase having the highest expression at the initial stages of pregnancy and type II deiodinase having the highest expression at the first trimester. The deiodinases are expressed throughout the fetus to maintain maternal THs levels in an appropriate range for the developing fetus [8].
3. Pregnancy causes the rate of glomerular filtration to rise, leading to an increase in renal clearance of iodine, so lower levels of iodine are in circulation. This stimulates the maternal thyroid, adding to the risk of hypothyroidism and goiter [4, 5]. The sodium-iodide symporter (NIS) plays an important role in iodine uptake into the mother's thyroid follicular cells and across the placenta. This transport into the fetal circulation is aided by pendrin, which, along with NIS, is expressed in the placenta, enabling the synthesis of THs by the fetal thyroid [9].
4. Levels of the human chorionic gonadotropin  $\beta$ -subunit increase during pregnancy, leading to a rise in free THs and lower TSH concentrations [3-5].
5. Thyroglobulin levels frequently increase in pregnancy, with subsequent pregnancy-associated goiters in 5-15% of cases [5].
6. To fulfill their role in fetal development, THs must be transported across the plasma membrane. There are at least six known TH plasma membrane transporters: MCT8, MCT10, LAT1, LAT2, OATP1A2, and OATP4A1. These proteins facilitate the maternofetal transfer of THs in early pregnancy and play a part in regulating trophoblast activity, helping to maintain equilibrium between cell apoptosis and proliferation [10].

In addition to physiological changes, environmental toxins e.g. dioxins and polychlorinated biphenyls can alter thyroid function during pregnancy [11]. Smoking is also linked to alterations in maternal and fetal thyroid function [12].

#### *The Developing Fetus*

The thyroid gland is the first gland that the growing embryo develops, and THs from the mother can be found in the embryo about four weeks into pregnancy [13, 14]. After 8-9 weeks into pregnancy, the fetus brain contains nuclear TH receptors, with levels comparable to those of adults found after 18 weeks [14].

In the first trimester, the THs affecting the development of the fetal central nervous system depend on maternal THs, which cross the placenta during this early stage of pregnancy. After about six weeks, the maternal free  $T_4$  stimulates neural progenitors to proliferate and migrate in the cerebral cortex, the hippocampus, and the medial ganglionic eminence of the fetus. By the 10-12<sup>th</sup> week, the fetal thyroid is able to accumulate iodine [15]. As the fetus moves into the second trimester, its thyroid begins its own hormone production, developing its complete hypothalamic-pituitary-thyroid system at about 20 weeks [13]. Besides neurogenesis and migration, THs are implicated in the growth of axons, arborization of dendrites, and formation of synapses. They also affect the differentiation and migration of glial cells and promote myelination [14].

Although the fetal thyroid gland starts to produce its own hormones in the second trimester, maternal THs continue to be implicated in neurodevelopment until delivery, when the fetal thyroid is fully mature [14]. Concentrations of  $T_4$  and  $fT_4$  in the fetal circulation progressively rise during pregnancy, achieving adult levels near the beginning of the third trimester, but low concentrations of  $T_3$  and  $fT_3$  are maintained during gestation and rise only at the end of gestation [16]. Clearly, maternal  $T_4$  concentrations in early pregnancy play a key role in providing the fetal cortex with THs, and they maintain this importance until delivery.

#### *Hypothyroidism and Hypothyroxinemia in Pregnancy*

##### *Definition*

Hypothyroidism occurs when not enough TH is produced [17]. Hypothyroidism is subdivided into three types, according to the etiology: primary, secondary, and tertiary. Primary hypothyroidism happens when the thyroid gland fails to produce THs [17], whereas secondary and tertiary hypothyroidism, often grouped and known as central hypothyroidism, are caused by damage in the hypothalamic-pituitary axis, leading to insufficient release of TRH and TSH [17]. The clinical presentation of hypothyroidism varies widely, and its symptoms are similar to those of other conditions, so its definition is primarily biochemical. Hypothyroidism can be mild or severe. Severe hypothyroidism, called overt or clinical hypothyroidism, is diagnosed when serum TSH concentrations are above normal, and  $fT_4$  is lower than the range considered normal [17]. Subclinical, or mild, hypothyroidism is diagnosed when TSH levels are above normal, but the  $fT_4$  value is within the normal range. Isolated maternal hypothyroxinemia in pregnancy is diagnosed when  $fT_4$  levels are lower than the normal range without elevated TSH levels [2].

### *Epidemiology*

The prevalence of overt hypothyroidism in pregnant women has been reported to range from 0.3 to 1.9% [1, 3, 18-20], with subclinical hypothyroidism being reported in 1.5-5% of pregnant women [1, 3, 21, 22]. Prevalence rates rose in 2011, after the American Thyroid Association (ATA) issued recommendations to use a TSH value of 2.5 mIU/ml as the upper end of the normal range in the initial trimester and 3.0 mIU/L as the upper limit in the last two trimesters [23]. Wide ranges in the prevalence of isolated hypothyroxinemia during pregnancy have been reported, from 1.3% on the low end all the way up to 25.4% [4]. These disparities are linked to differences in diagnostic criteria, maternal iodine intake, gestational age, or method of measuring fT<sub>4</sub> [3].

### *Etiology*

Globally, the most common factor in hypothyroidism in pregnancy is iodine deficiency, but in countries with adequate levels of iodine, the most frequent reason for this condition is autoimmune thyroiditis or Hashimoto's thyroiditis [24]. Isolated hypothyroxinemia is most frequently caused by marginal iodine deficiency in the diet [3].

While iodine deficiency is the most common etiology for gestational hypothyroidism, other risk factors have now been identified [1, 4, 20-22, 24]: >30 years of age, history of thyroid dysfunction (goiter; positive thyroid antibodies), clinical symptoms or signs of hypo-hyperthyroidism, family history of autoimmune thyroid diseases or thyroid dysfunction, history of diseases known to affect thyroid function, diabetes mellitus type 1 or other autoimmune disorders, multigravida, miscarriage, premature labor, fertility problems, use of medications like amiodarone, thalidomide, oral tyrosine kinase inhibitors, interferon, bexarotene, perchlorate, ethionamide, rifampin, phenytoin, phenobarbital, carbamazepine, interleukin-2, and lithium, radiotherapy of the head and neck region, thyroid surgery, recent (in the past 6 weeks) exposure to radiographic iodinated contrast, morbid obesity, and living in a region characterized by moderate to severe iodine deficiency.

### *Diagnosis*

#### *Clinical Signs and Symptoms*

There are no clear symptoms of isolated hypothyroxinemia and subclinical hypothyroidism. Those of overt hypothyroidism, however, are noticeable but quite nonspecific, affecting various organ systems:

1. Integumentary: Dry, pale, and thick skin, coarse hair, hoarseness deeper voice, enlargement of the tongue, facial puffiness, swollen eyelid, peripheral edema, cold intolerance, goiter, and hypohidrosis.
2. Gastrointestinal: Constipation, low appetite, and weight gain disproportionate to gestational age.
3. Cardiovascular: Diastolic hypertension, bradycardia, cardiomegaly, and pericardial effusions.
4. Musculoskeletal: myasthenia, decreased osteotendonous reflexes, cramps, stiffness, fatigue, and lethargy.
5. Neurological: Decreased attention span, impaired memory, altered mood, and depression.
6. Reproductive: low libido [17, 25].

#### *Laboratory Diagnosis*

With the increasing metabolic demands women face during pregnancy, the normal range of results for thyroid function testing is different from those of healthy nonpregnant women. Therefore, in 2011 the ATA proposed reference limits for TSH and fT<sub>4</sub> that are specific to pregnant women, even going so far as to suggest reference levels for each trimester of pregnancy [2]. However, more recent research has called into question these specific TSH reference limits. For instance, research in India, East Asia, and the Netherlands have found the upper reference limit of TSH to be only modestly lower than healthy nonpregnant women [1]. The general ATA guidelines suggest a diagnosis of primary overt maternal hypothyroidism when the TSH value is above the upper limit of the gestational reference range (>4.0 mIU/L) and serum fT<sub>4</sub> levels are lower than expected, or when the TSH levels reach  $\geq 10.0$  mIU/L, regardless of serum fT<sub>4</sub> levels [1]. Subclinical maternal hypothyroidism is diagnosed when the serum TSH concentration is between 4.0-10 mIU/L and fT<sub>4</sub> level is in the normal range [1]. Isolated maternal hypothyroxinemia is diagnosed when a normal TSH level is accompanied by an fT<sub>4</sub> level in the lower 2.5<sup>th</sup>-5<sup>th</sup> percentile of the reference limits [1].

As the considerable geographic and ethnic variations in TSH concentrations during pregnancy have come to light, the ATA recommends using local reference ranges tailored specifically for each trimester and varying according to population, medical center, or even laboratory facility. However, if these are lacking, APA advises that 4.0 mIU/L be used as the upper reference limit of TSH in the first trimester, returning gradually towards the nonpregnant normal TSH range (0.45-4.5 mIU/L) [17, 18] as the pregnancy progresses in the second and third trimester [1].

Further variation in the assessment of hypothyroidism stems from the way fT<sub>4</sub> levels are interpreted, which depends on each patient's iodine intake and the type of assay used. The recommended method is to measure fT<sub>4</sub> in the dialysate or ultrafiltrate of serum samples, using online solid-phase extraction-liquid chromatography/tandem mass spectrometry [1, 2].

In around one-third to two-thirds of pregnant women with high levels of TSH, thyroid antibodies (TAb) are found. Pregnant women with thyroid peroxidase antibodies (TPOAb) may have a higher risk of adverse outcomes [26], so the ATA recommends TPOAb evaluation when deciding on treatment [4].

#### *Treatment*

Daily recommended intake of iodine (potassium iodide) is 150 µg for non-pregnant women or those planning to be and 250 µg for pregnant or lactating women [1].

For women who are trying to conceive, treatment with levothyroxine is the best way to preempt overt hypothyroidism, aiming to reduce TSH levels to <2.5 mIU/L [3]. In pregnancy, requirements for thyroxine gradually grow from 4-6 to 16-20 weeks. These higher T<sub>4</sub> requirements continue until delivery, so it is crucial to monitor TSH and fT<sub>4</sub> values and adjust therapy as needed [27].

The APA guidelines also include a recommendation that euthyroid women who suspect they are pregnant and have already started taking levothyroxine daily take two extra doses per week (20-30% increase) immediately. However, preconception levels of TSH and the cause of any maternal hypothyroidism may call for modification of treatment with levothyroxine [1-3]. During the first half of pregnancy, TSH levels must be checked once a month, and at least once between weeks 26-32 [28].

If a woman has overt hypothyroidism after she becomes pregnant, she should start taking levothyroxine right away to bring the thyroid function test results to within the normal reference range. This thyroid function test should be re-administered within 30-40 days, and subsequently every 4-6 weeks, with the dose of levothyroxine being modified as needed based on these test results [3]. After pregnancy, the amount of levothyroxine given should be lowered to pregestational levels, and serum TSH levels should be assessed after six weeks. However, more than half of women with Hashimoto's thyroiditis need more TH in the postpartum period than they did before pregnancy [1, 2, 29].

Levothyroxine therapy is generally recommended for pregnant women with subclinical hypothyroidism only if they are TPOAb positive in order to maintain normal gestational TSH concentrations [1, 2, 30]. However, recommendations from the Italian Society of Endocrinology (ISE) and the Italian Thyroid Association (ITA) are broader, suggesting that pregnant women who test positive for TPOAb and have TSH values of 2.5-4.0 mIU/L be given levothyroxine, especially in the first trimester, to preempt rising serum TSH levels [31]. The ATA recommends that levothyroxine therapy for women with subclinical hypothyroidism and negative TPOAb status be used following their 2017 guidelines [1], but the ISE and ITA recommend levothyroxine in these cases because negative TPOAb results have been reported in a significant number of patients with chronic autoimmune thyroiditis because of maternal immunosuppression [31]. In cases where levothyroxine is given for subclinical hypothyroidism during pregnancy, a reevaluation of thyroid function should be conducted after delivery to determine if therapy should be continued [32]. Treatment with levothyroxine therapy is not advised for TPOAb-negative patients with TSH values in the normal range.

Treatment with levothyroxine for patients with isolated hypothyroxinemia is not recommended due to lack of evidence supporting its use [1, 3, 33].

### *Complications in Pregnancy*

Maternal iodine deficiency and low TH levels are implicated in various complications in pregnancy and negative outcomes linked to the growth and neurodevelopment of the fetus.

#### *1. Euthyroid women with positive TPOab status*

Various studies have found higher risk of miscarriage [34], premature delivery [35], perinatal mortality [36], postpartum thyroid dysfunction [37], postpartum depression [38], neonatal respiratory distress syndrome [39], and delays in cognitive and psychomotor development in their children [40].

#### *2. Women with overt hypothyroidism*

In this population, there is a greater risk of miscarriage, stillbirth, gestational anemia, gestational arterial hypertension, preeclampsia, placental abruption, threatened preterm labor, premature delivery, heavy bleeding after delivery, heart failure, low birth weight, and heightened neonatal respiratory distress [33]. Placental dysfunction can cause intrauterine growth to be restricted, leading to low fetal TH circulation and reduced expression of TH receptors in the fetal brain, which may be linked in part to mild neurodevelopment impairment [41]. Altered behavior and impaired cognitive development, especially related to attention, visual processing, and gross motor skills, have been reported in children whose mothers were hypothyroid and iodine-deficient in early pregnancy [35, 42]. Studies have reported attention disorders, delays in psychomotor and language development, and an average IQ score seven points lower in children of women who did not receive treatment for hypothyroidism compared to children whose mothers had normal thyroid function [3, 43, 44].

#### *3. Women with subclinical hypothyroidism*

In this population, studies have found a greater risk of several adverse outcomes including miscarriage, premature delivery, preeclampsia, breech birth, small for gestational age and lower birth weight, and a higher rate of fetal death [21, 22, 45, 46]. Some research also suggests that children of women who had subclinical hypothyroidism while pregnant have impaired neuropsychological vision development [2, 13, 44, 46]. However, not all research has found a correlation between subclinical hypothyroidism and adverse outcomes [30].

#### *4. Women with isolated hypothyroxinemia*

In this population, some research suggests an association between isolated hypothyroxinemia and preterm delivery, premature rupture of fetal membranes, and above-average weight at birth [47]. Other research focusing on the initial 20 weeks of pregnancy has found that diagnosis of isolated hypothyroxinemia in this period is linked to fetal distress, musculoskeletal abnormalities, and small for gestational age [46]. When diagnosis occurs in the first 12 weeks of

pregnancy, it has been linked to delayed psychomotor function when the children are 12 and 24 months old as well as a delay in expressive language when they are 18-30 months old [45]. However, other research has found no heightened risk of adverse outcomes in the children whose mothers had isolated hypothyroxinemia [48].

Given the link between elevated TSH values in pregnant women and negative outcomes such as impaired psychomotor development in their children [49], the effect of levothyroxine on pregnant women diagnosed with subclinical hypothyroidism has been studied through randomized trials. The results indicate that levothyroxine therapy improves pregnancy outcomes and lowers the rate of preterm delivery [30] in women who are positive for TPOAb and have TSH levels  $>2.5$  mIU/L. However, no significant impact on children's intellectual development at three [50] and five years of age has been found, although these results may have been affected by the treatment with levothyroxine being started late, typically in the 17<sup>th</sup> week of pregnancy [51].

#### *Screening*

The decision to test for hypothyroidism either before pregnancy or in the first trimester should consider the likelihood of detecting changes in maternal TH concentrations or the correlation between these changes and the higher risk of negative outcomes during pregnancy and in the cognitive development of the children, but since it is still uncertain what effect treatment for thyroid dysfunction has on the risk of adverse outcomes, universal screening for TSH and thyroid antibodies remains controversial. More research is needed to assess the impact of first-trimester levothyroxine therapy on perinatal outcomes and intellectual development of the child.

In 2002, the American Association of Clinical Endocrinologists advised TSH testing for all women planning to become pregnant or in the first trimester as a routine practice [52]. In contrast, the 2017 ATA guidelines suggest restricting TSH screening to expectant women known to be a high risk [2, 4, 17]. However, if only high-risk patients are screened, 30% of women with hypothyroidism would not be detected [22].

#### *Newborns*

In the first week following delivery, the TSH level in neonates increases, triggering increased production of  $ft_4$  by the thyroid gland. This synthesis of THs occurs when there is a sufficient amount of pre- and postnatal iodine [53]. Neonatal hypothyroidism—reported in one in 3,000-4,000 births—can be either transient or permanent. Hypothyroidism of a transient nature can be brought on by several factors: low or (paradoxically) high levels of iodine, maternal intake of antithyroid medications and goitrogens while pregnant, transport of TAb from the mother across the placenta that obstruct the neonatal TSH receptors, very low birth weight for gestational age, and premature delivery. Despite its temporary nature, however, transient hypothyroidism can have deleterious effects in infants, especially on their neurological development, so it is advisable to diagnose this early so that it can be treated [53].

There are also greater risks of complications in infants of women with autoimmune thyroid disease, most commonly Hashimoto's disease, depending on the kind and amount of transplacental TAb [53]. Evidence suggests a link between autoimmune thyroid disease in the mother and transient congenital hypothyroidism in the newborn.

Screening for TSH and  $ft_4$  levels in newborns should be carried out 48 hours after delivery and again in the period between weeks 2 and 4 for infants whose initial TSH values were  $>6$  mUI/L, especially when their mothers have autoimmune thyroid disease [53, 54].

#### *Thyroid Dysfunction and COVID-19*

The novel coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is linked to high morbidity and mortality rates with effective therapy being limited. Like others in the coronavirus family, the SARS-CoV-2 virus attacks the body, using angiotensin-converting enzyme 2 (ACE2) receptors to enter cells, as these receptors interact with the transmembrane protease serine 2 (TMPRSS2) [55]. Of interest in this review, ACE2 and TMPRSS2 expression levels in the thyroid gland are high, to an extent greater than that seen in the lungs [55].

#### *Clinical Manifestations*

Patients with COVID-19 may be asymptomatic cases, or the disease may manifest itself in a variety of ways, ranging from mild upper respiratory tract infection to severe cases of pneumonia and acute respiratory distress that can lead to death [56].

The WHO lists those who are more vulnerable as people with certain comorbidities, but this general guidance does not include COVID-19 risks for people with pre-existing thyroid dysfunction. Likewise, the American Thyroid Association has not recommended specific measures for hypothyroid patients but emphasizes the need to limit the transmission of COVID-19 and advises this group of patients to maintain their prescribed treatment [57].

Evaluation of thyroid function for COVID-19 is not part of the WHO's guidelines for clinical management [58]. However, changes in thyroid function were reported during the previous SARS-CoV outbreak [59, 60]. A study carried out during the 2003 SARS outbreak found significantly reduced serum  $T_3$  and  $T_4$  concentrations in patients with SARS compared to healthy controls in both the progression and recovery stages of the disease, with low  $T_3$  concentrations associated with disease severity [59]. Leow *et al.* evaluated 61 SARS-CoV survivors three months after recovery, looking for hormonal abnormalities and found that four (6.7%) of the patients had developed biochemical hypothyroidism. The three patients who

developed central hypothyroidism saw their condition disappear three to nine months later, but the single patient with primary hypothyroidism (caused by new-onset chronic lymphocytic thyroiditis) needed permanent T<sub>4</sub> treatment [60]. Another study on patients with SARS found significant damage to the follicular epithelial and parafollicular cells of their thyroid glands [61]. Further research by Wei *et al.* found a reduction in the number of TSH-positive cells and their staining immunoreactivity in the pituitary of SARS patients, suggesting that lower TSH levels might be linked to the changes in TSH-secreting cells in the pituitary [62].

Chen *et al.* observed reduced TSH and T<sub>3</sub> concentrations in patients with COVID-19, with a positive correlation between COVID-19 severity and the extent of the TSH and T<sub>3</sub> reduction [63]. In addition, patients with severe and critical COVID-19 had serum TSH concentrations that were significantly lower than those in patients with non-COVID-19 pneumonia, when the severity of disease was comparable, suggesting COVID-19 may have a unique impact on cells that secrete TSH. A recent study also reported lower TSH and fT<sub>4</sub> levels in patients with COVID-19 compared to those without COVID-19 [64]. The most probable reason for these reported alterations is nonthyroidal illness syndrome, in which reduced total T<sub>4</sub> and fT<sub>3</sub> values are seen in conjunction with higher reverse T<sub>3</sub> values without an elevation of TSH. In longer or more critical periods of illness, overall lower TSH, fT<sub>4</sub>, and fT<sub>3</sub> values are seen [65]. TSH suppression is likely linked to increased levels of proinflammatory cytokines like interleukin-6, known to be negatively correlated with TSH. Cortisol, with its link to TSH secretion, may also play a role [66]. Increased endogenous cortisol secretion in patients with COVID-19 may act as a TSH suppressant [67]. A third potential explanation for the reported changes in thyroid function in the presence of COVID-19 might be a direct cytopathic effect of SARS-CoV-2 on thyrotrophs since the virus binds with the receptor ACE2, which is expressed in the pituitary [68]. Importantly, regardless of the factor involved in the reported reduction in TSH secretion, subsequent testing after recovery revealed a return to baseline TSH values, suggesting the changes in thyroid biomarkers are transient and reversible after COVID-19.

Alterations in the immune system occur during pregnancy, with more severe symptoms stemming from the reaction to viral infections. This immunological adaptation helps the woman to avoid rejection of the fetal semi-allograft [69], but as this occurs through the suppression of T-cell activity, women are more susceptible to viral infections during pregnancy [70]. The circulatory and respiratory systems also change during pregnancy, which could lead to more adverse clinical outcomes when viral infection occurs [71].

Thyroid disorders are common during pregnancy, with concern for their own health and that of their fetuses prompting patients to seek advice from physicians [72]. This concern often escalates to anxiety and even fear during infectious outbreaks [73].

Research has shown a clear link between depression and anxiety during pregnancy and adverse outcomes both on the pregnancy and on the child's subsequent development [74]. In their review of thyroid disorders and anxiety, Simon *et al.* (2002) found an association between altered mood and thyroid dysfunction [75]. A subsequent meta-analysis of 20 studies revealed a risk of thyroid disease to be significantly higher in people with anxiety being inversely proportional to TSH values [76]. In addition, numerous cross-sectional studies have found a higher risk of anxiety or depression in individuals with thyroid disorders [77]. For the most part, these studies have centered on the association between depression or anxiety disorders and TSH levels or overt hypothyroidism. More recently, however, the connection between mood alterations and isolated hypothyroxinemia, and fT<sub>3</sub> or fT<sub>4</sub> levels has also been investigated. Women who were pregnant during the COVID-19 pandemic were found to have elevated fT<sub>3</sub> and lower fT<sub>4</sub>, were more likely to develop isolated hypothyroxinemia, and had non-significantly higher TSH levels compared to pregnant women before the pandemic [78], suggesting that anxiety triggered by the COVID-19 pandemic during early pregnancy had a significant impact on maternal thyroid status [78]. One possible mechanism for this association is that anxiety magnifies the TSH enhancement of fT<sub>4</sub> to fT<sub>3</sub> conversion [79], but additional investigation is required to confirm this.

Presently, no evidence suggests a higher risk of COVID-19 in the population with thyroid disorders than in the euthyroid population or that thyroid disorders lead to worse outcomes for patients who have COVID-19. A study of >3,000 adults with COVID-19 revealed no link between hypothyroidism and the risk of COVID-related hospitalization, ventilation, or death [80]. Studies have shown that there is no correlation between well-controlled hypothyroidism and greater risk of infection; however, some evidence suggests that patients with poorly managed hypothyroidism may have a higher risk of infection [81]. The British Thyroid Association, the Society for Endocrinology (BTA/SFE), and the ATA all urge patients with thyroid dysfunction to stay on their prescribed thyroid medications until the COVID-19 pandemic is over [57] to lower any chance of thyroid dysregulation [82], which might worsen COVID-19 outcomes.

## Conclusion

The importance of understanding how THs work cannot be overstated. It is also crucial to understand how changes that occur throughout pregnancy work to ensure sufficient levels of these hormones, as THs are involved in the onset and progression of pregnancy and play a critical role in the neural development of the embryo, fetus, and neonate.

To diagnose hypothyroidism, the ATA has recommended separate specific benchmarks for different populations: non-pregnant women and pregnant women, with different reference limits at each trimester of pregnancy. Using these recommended stricter TSH benchmarks for pregnant women may result in a higher incidence of gestational thyroid disorders. Universal screening for thyroid dysfunction in the first trimester has been proposed despite the cost as this

identification of hypothyroid women would allow timely treatment and potential decrease in adverse perinatal and neonatal outcomes, with subsequent health and economic benefits.

Although the effectiveness of universal screening in lowering adverse perinatal outcomes remains in question, studying screening for thyroid function in each population, not just in at-risk women could offer a key cost-benefit ratio. Assessment of the impact of early levothyroxine therapy (before 16-20 weeks gestation) on the risk during pregnancy and to the child after birth is also important because the current evidence is restricted to levothyroxine therapy begun after 17 weeks when the fetal thyroid begins to produce thyroid hormones.

Early evidence suggests that hypothyroidism is not a risk factor for more severe outcomes in COVID-19 patients, so precautions or consultations beyond the usual measures are not necessary. However, additional studies on how COVID-19 may affect the thyroid gland and function are warranted.

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## References

- Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*. 2017;27(3):315-89. doi:10.1089/thy.2016.0457
- Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid*. 2011;21(10):1081-125. doi:10.1089/thy.2011.0087
- Teng W, Shan Z, Patil-Sisodia K, Cooper DS. Hypothyroidism in pregnancy. *Lancet Diabetes Endocrinol*. 2013;1(3):228-37. doi:10.1016/S2213-8587(13)70109-8
- Yazbeck CF, Sullivan SD. Thyroid disorders during pregnancy. *Med Clin N Am*. 2012;96(2):235-56. doi:10.1016/j.mcna.2012.01.004
- Fantz CR, Dagogo-Jack S, Ladenson JH, Gronowski AM. Thyroid function during pregnancy. *Clin Chem*. 1999;45(12):2250-8.
- Cignini P, Cafà EV, Giorlandino C, Capriglione S, Spata A, Dugo N. Thyroid physiology and common diseases in pregnancy: review of literature. *J Prenat Med*. 2012;6(4):64-71.
- Lambot N, Lybaert P, Boom A, Delogne-Desnoeck J, Vanbellinghen AM, Graff G, et al. Evidence for a clathrin-mediated recycling of albumin in human term placenta. *Biol Reprod*. 2006;75(1):90-7. doi:10.1095/biolreprod.105.050021
- Dentice M, Marsili A, Zavacki A, Larsen PR, Salvatore D. The deiodinases and the control of intracellular thyroid hormone signaling during cellular differentiation. *Biochim Biophys Acta*. 2013;1830(7):3937-45. doi:10.1016/j.bbagen.2012.05.007
- Degrelle SA, Guibourdenche J, Galland F, Bidart JM, Fournier T, Evain-Brion D. Iodide transporters expression in early human invasive trophoblast. *Placenta*. 2013;34(1):29-34. doi:10.1016/j.placenta.2012.11.002
- Loubiere LS, Vasilopoulou E, Bulmer JN, Taylor PM, Stieger B, Verrey F, et al. Expression of thyroid hormone transporters in the human placenta and changes associated with intrauterine growth restriction. *Placenta*. 2010;31(4):295-304. doi:10.1016/j.placenta.2010.01.013
- Koopman-Esseboom C, Morse DC, Weisglas-Kuperus N, Lutkeschipholt IJ, Van Der Paauw CG, Tuinstra LG, et al. Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. *Pediatr Res*. 1994;36(4):468-73. doi:10.1203/00006450-199410000-00009
- Shields B, Hill A, Bilous M, Knight B, Hattersley AT, Bilous RW, et al. Cigarette smoking during pregnancy is associated with alterations in maternal and fetal thyroid function. *J Clin Endocrinol Metab*. 2009;94(2):570-4. doi:10.1210/jc.2008-0380
- de Escobar GM, Obregón MJ, del Rey FE. Maternal thyroid hormones early in pregnancy and fetal brain development. *Best Pract Res Clin Endocrinol Metabol*. 2004;18(2):225-48. doi:10.1016/j.beem.2004.03.012
- Williams GR. Neurodevelopmental and neurophysiological actions of thyroid hormone. *J Neuroendocrinol* 2008;20(6):784-94. doi:10.1111/j.1365-2826.2008.01733.x
- Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. *N Engl J Med*. 1994;331(16):1072-8. doi:10.1056/NEJM199410203311608
- Thorpe-Beeston JG, Nicolaidis KH, Felton CV, Butler J, McGregor AM. Maturation of the secretion of thyroid hormone and thyroid-stimulating hormone in the fetus. *N Engl J Med*. 1991;324(8):532-6. doi:10.1056/NEJM199102213240805
- Brenta G, Vaisman M, Sgarbi JA, Bergoglio LM, Andrada NC, Bravo PP, et al. Task Force on Hypothyroidism of the Latin American Thyroid Society (LATS). Clinical practice guidelines for the management of hypothyroidism. *Arq Bras Endocrinol Metabol*. 2013;57(4):265-91. doi:10.1590/s0004-27302013000400003
- Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87(2):489-99. doi:10.1210/jcem.87.2.8182
- Lazarus JH. Screening for thyroid dysfunction in pregnancy: is it worthwhile? *J Thyroid Res*. 2011;2011:397012. doi:10.4061/2011/397012

20. Diéguez M, Herrero A, Avello N, Suárez P, Delgado E, Menéndez E. Prevalence of thyroid dysfunction in women in early pregnancy: does it increase with maternal age? *Clin Endocrinol (Oxf)*. 2016;84(1):121-6. doi:10.1111/cen.12693
21. Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, et al. Maternal thyroid deficiency and pregnancy complications: implications for population screening. *J Med Screen*. 2000;7(3):127-30. doi:10.1136/jms.7.3.127
22. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, et al. Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol*. 2005;105(2):239-45. doi:10.1097/01.AOG.0000152345.99421.22
23. Li C, Shan Z, Mao J, Wang W, Xie X, Zhou W, et al. Assessment of thyroid function during first-trimester pregnancy: what is the rational upper limit of serum TSH during the first trimester in Chinese pregnant women? *J Clin Endocrinol Metab*. 2014;99(1):73-9. doi:10.1210/jc.2013-1674
24. Peeters RP. Subclinical Hypothyroidism. *N Engl J Med*. 2017;376(26):2556-65. doi:10.1056/NEJMcp1611144
25. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract*. 2012;18(6):988-1028. doi:10.4158/EP12280.GL
26. Korevaar TI. Evidence-based tightrope alking: the 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*. 2017;27(3):309-11. doi:10.1089/thy.2017.29040.tko
27. Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med*. 2004;351(3):241-9. doi:10.1056/NEJMoa040079
28. Yassa L, Marqusee E, Fawcett R, Alexander EK. Thyroid hormone early adjustment in pregnancy (the Therapy) trial. *J Clin Endocrinol Metab*. 2010;95(7):3234-41. doi:10.1210/jc.2010-0013
29. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, et al. Management of thyroid dysfunction during pregnancy and postpartum: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97(8):2543-65. doi:10.1210/jc.2011-2803
30. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Alavi Majid H, Azizi F. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. *Eur J Endocrinol*. 2017;176(2):253-65. doi:10.1530/EJE-16-0548
31. Rotondi M, Chiovato L, Pacini F, Bartalena L, Vitti P. Management of subclinical hypothyroidism in pregnancy: a comment from the Italian society of Endocrinology and the Italian thyroid association to the 2017 American thyroid association guidelines- "the Italian way". *Thyroid*. 2018;28(5):551-5. doi:10.1089/thy.2017.0424
32. Shields BM, Knight BA, Hill AV, Hattersley AT, Vaidya B. Five-year follow-up for women with subclinical hypothyroidism in pregnancy. *J Clin Endocrinol Metab*. 2013;98(12):E1941-5. doi:10.1210/jc.2013-2768
33. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European Thyroid Association Guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J*. 2014;3(2):76-94. doi:10.1159/000362597
34. Stagnaro-Green A, Roman SH, Cobin RH, El-Harazy E, Alvarez-Marfany M, Davies TF. Detection of at-risk pregnancy by means of highly sensitive assays for thyroid autoantibodies. *JAMA*. 1990;264(11):1422-5.
35. Glinooer D, Soto MF, Bourdoux P, Lejeune B, Delange F, Lemone M. Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. *J Clin Endocrinol Metab*. 1991;73(2):421-7. doi:10.1210/jcem-73-2-421
36. Mannisto T, Vaarasmaki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, et al. Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. *J Clin Endocrinol Metab*. 2009;94(3):772-9. doi:10.1210/jc.2008-1520
37. Premawardhana LD, Parkes AB, John R, Harris B, Lazarus JH. Thyroid peroxidase antibodies in early pregnancy: utility for prediction of postpartum thyroid dysfunction and implications for screening. *Thyroid*. 2004;14(8):610-5. doi:10.1089/1050725041692828
38. Groer MW, Vaughan JH. Positive thyroid peroxidase antibody titer is associated with dysphoric moods during pregnancy and postpartum. *J Obstet Gynecol Neonatal Nurs*. 2013;42(1):E26-32. doi:10.1111/j.1552-6909.2012.01425.x
39. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Thyroid antibody positivity in the first trimester of pregnancy is associated with negative pregnancy outcomes. *J Clin Endocrinol Metab*. 2011;96(6):E920-4. doi:10.1210/jc.2011-0026
40. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, et al. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. *Clin Endocrinol (Oxf)*. 2010;72(6):825-9. doi:10.1111/j.1365-2265.2009.03743.x
41. Chan SY, Franklyn JA, Pemberton HN, Bulmer JN, Visser TJ, McCabe CJ, et al. Monocarboxylate transporter 8 expression in the human placenta: the effects of severe intrauterine growth restriction. *J Endocrinol*. 2006;189(3):465-71. doi:10.1677/joe.1.06582
42. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. *Thyroid*. 2002;12(1):63-8. doi:10.1089/105072502753451986
43. Morreale de Escobar G, Obregon MJ, Escobar del Rey F. Role of thyroid hormone during early brain development. *Eur J Endocrinol*. 2004;151(Suppl 3): U25-37. doi:10.1530/eje.0.151u025
44. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Eng J Med*. 1999;341(8):549-55. doi:10.1056/NEJM199908193410801
45. Pop VJ, Brouwers EP, Wijnen H, Oei G, Essed GG, Vader HL. Low concentrations of maternal thyroxine during early gestation a risk factor of breech presentation? *BJOG*. 2004;111(9):925-30. doi:10.1111/j.1471-0528.2004.00213.x
46. Su PY, Huang K, Hao JH, Xu YQ, Yan SQ, Li T, et al. Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: a prospective population-based cohort study in China. *J Clin Endocrinol Metab*. 2011;96(10):3234-41. doi:10.1210/jc.2011-0274
47. León G, Murcia M, Rebagliato M, Álvarez-Pedrerol M, Castilla AM, Basterrechea M, et al. Maternal thyroid dysfunction during gestation, preterm delivery, and birthweight. The infancia y medio ambiente cohort, Spain. *Paediatr Perinat Epidemiol*. 2015;29(2):113-22. doi:10.1111/ppe.12172
48. Craig WY, Allan WC, Kloza EM, Pulkkinen AJ, Waisbren S, Spratt DI, et al. Mid-gestational maternal free thyroxine concentration and offspring neurocognitive development at age two years. *J Clin Endocrinol Metab*. 2012;97(1):E22-8. doi:10.1210/jc.2011-1772



49. Fan X, Wu L. The impact of thyroid abnormalities during pregnancy on subsequent neuropsychological development of the offspring: a meta-analysis. *J Matern Fetal Neonatal Med.* 2016;29(24):3971-6. doi:10.3109/14767058.2016
50. Lazarus JH, Bestwick JP, Channon S, Paradise R, Maina A, Rees R, et al. Antenatal thyroid screening childhood cognitive function. *N Engl J Med.* 2012;366(6):493-501. doi:10.1056/NEJMoal106104
51. Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, et al. Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. *N Eng J Med.* 2017;376(9):815-25. doi:10.1056/NEJMoal1606205
52. Baskin HJ, Cobin RH, Duick DS, Gharib H, Guttler RB, Kaplan MM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract.* 2002;8(6):457-69.
53. Ozdemir H, Akman I, Coskun S, Demirel U, Turan S, Bereket A, et al. Maternal thyroid dysfunction and neonatal thyroid problems. *Int J Endocrinol.* 2013;2013:987843. doi:10.1155/2013/987843
54. Molina MC, Martín MJ, de Juan Ruiz J, Segura SA. Maternal autoimmune thyroid disease: relevance for the newborn. *Med Clin (Barc).* 2015;144(7):297-303. doi:10.1016/j.medcli.2013.10.024
55. Ziegler CG, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell.* 2020;181(5):1016-35. doi:10.1016/j.cell.2020.04.035
56. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan China. *Lancet.* 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5
57. Novel Coronavirus (COVID-19) and the Thyroid. Available from: <https://www.thyroid.org/covid-19/statement-covid-19/> (accessed June 4, 2020).
58. World Health Organization. (2020) Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance. Available from: (27 May 2020) <https://apps.who.int/iris/handle/10665/331446>.
59. Wang W, Ye YX, Yao H. Evaluation and observation of serum thyroid hormone and parathyroid hormone in patients with severe acute respiratory syndrome. *J Chin Antituberculous Assoc.* 2003;25:232-4. doi:10.1371/journal.pone.0249421
60. Leow MK, Kwek DS, Ng AW, Ong KC, Kaw GJ, Lee LS. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). *Clin Endocrinol (Oxf).* 2005;63(2):197-202. doi:10.1111/j.1365-2265.2005.02325.x
61. Wei L, Sun S, Xu CH, Zhang J, Xu Y, Zhu H, et al. Pathology of the thyroid in severe acute respiratory syndrome. *Hum Pathol.* 2007;38(1):95-102. doi:10.1016/j.humpath.2006.06.011
62. Wei L, Sun S, Zhang J, Zhu H, Xu Y, Ma Q, et al. Endocrine cells of the adenohypophysis in severe acute respiratory syndrome (SARS). *Biochem Cell Biol.* 2010;88(4):723-30. doi:10.1139/O10-022
63. Chen M, Zhou W, Xu W. Thyroid Function Analysis in 50 Patients with COVID-19: A Retrospective Study. *Thyroid.* 2020;31(1):8-11. doi:10.1089/thy.2020.0363
64. Khoo B, Tan T, Clarke SA, Mills EG, Patel B, Modi M, et al. Thyroid Function Before, During, and After COVID-19. *J Clin Endocrinol Metab.* 2021;106(2):e803-11. doi:10.1210/clinem/dgaa830
65. Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. *Thyroid.* 2014;24(10):1456-65. doi:10.1089/thy.2014.0201
66. Dogansen SC, Yalin GY, Canbaz B, Tanrikulu S, Yarman S. Dynamic changes of central thyroid functions in the management of Cushing's syndrome. *Arch Endocrinol Metab.* 2018;62(2):164-71. doi:10.20945/2359-3997000000019
67. Tan T, Khoo B, Mills EG, Phylactou M, Patel B, Eng PC, et al. Association between high serum total cortisol concentrations and mortality from COVID-19. *Lancet Diabetes Endocrinol.* 2020;8(8):659-60. doi:10.1016/S2213-8587(20)30216-3
68. Lazartigues E, Qadir MMF, Mauvais-Jarvis F. Endocrine Significance of SARS-CoV-2's Reliance on ACE2. *Endocrinol.* 2020;161(9):bqaa108. doi:10.1210/endo/bqaa108
69. Moleti M, Sturniolo G, Di Mauro M, Russo M, Vermiglio F. Autoimmune thyroid diseases and pregnancy. *Annals of Thyroid.* 2018;3(7):311-8. doi:10.1038/nrendo.2010.46
70. Pazos M, Sperling RS, Moran TM, Kraus TA. The influence of pregnancy on systemic immunity. *Immunol Res.* 2012;54(1-3):254-61. doi:10.1007/s12026-012-8303-9
71. Rasmussen SA, Smulian JC, Lednický JA, Wen TS, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) and Pregnancy: What obstetricians need to know. *Am J Obstet Gynecol.* 2020;222(5):415-26. doi:10.1016/j.ajog.2020.02.017
72. Saccone G, Florio A, Aiello F, Venturella R, De Angelis MC, Locci M, et al. Psychological impact of coronavirus disease 2019 in pregnant women. *Am J Obstet Gynecol.* 2020;223(2):293-5. doi:10.1016/j.ajog.2020.05.003
73. Horton R. Offline: 2019-nCoV-"A desperate plea". *Lancet.* 2020;395(10222):400. doi:10.1016/s0140-6736(20)30299-3
74. Dennis CL, Falah-Hassani K, Shiri R. Prevalence of antenatal and postnatal anxiety: systematic review and meta-analysis. *Br J Psychiatry J Ment Sci.* 2017;210(5):315-23. doi:10.1192/bjp.bp.116.187179
75. Simon NM, Blacker D, Korbly NB, Sharma SG, Worthington JJ, Otto MW, et al. Hypothyroidism and hyperthyroidism in anxiety disorders revisited: new data and literature review. *J Affect Disord.* 2002;69(1-3):209-17. doi:10.1016/S0165-0327(01)00378-0
76. Fischer S, Ehlert U. Hypothalamic-pituitary-thyroid (HPT) axis functioning in anxiety disorders. A systematic review. *Depress Anxiety.* 2018;35(1):98-110. doi:10.1002/da.22692
77. Mohammad MY, Bushulaybi NA, AlHumam AS, AlGhamdi AY, Aldakhil HA, Alumair NA, et al. Prevalence of depression among hypothyroid patients attending the primary healthcare and endocrine clinics of King Fahad Hospital of the University (KFHU). *J Family Med Prim Care.* 2019;8(8):2708-13. doi:10.4103/jfmpc.jfmpc\_456\_19
78. Lin TT, Zhang C, Zhang HQ, Wang Y, Chen L, Dennis CL, et al. Thyroid Hormone Changes in Early Pregnancy Along with the COVID-19 Pandemic. *Front Endocrinol.* 2020;11:606723. doi:10.3389/fendo.2020.606723
79. Quinlan P, Horvath A, Wallin A, Svensson J. Low serum concentration of free triiodothyronine (FT3) is associated with increased risk of Alzheimer's disease. *Psychoneuroendocrinology.* 2019;99:112-9. doi:10.1016/j.psyneuen.2018.09.002
80. van Gerwen M, Alsen M, Little C, Barlow J, Naymagon L, Tremblay D, et al. Outcomes of Patients with Hypothyroidism and COVID-19: A Retrospective Cohort Study. *Front Endocrinol.* 2020;11:565. doi:10.3389/fendo.2020.00565

81. Mayer D, Miller-Hänisch B, Böckh A, Hehrmann R. Fulminant meningococcal meningitis and sepsis associated with severe hypothyroidism caused by autoimmune (Hashimoto) thyroiditis. *Exp Clin Endocrinol Diabetes*. 1997;105(Suppl 4):80. doi:10.1055/s-0029-1211942
82. BTA/SGE statement regarding issues specific to thyroid dysfunction during the COVID-19 pandemic. Available from: <https://www.british-thyroid-association.org/sandbox/bta2016/management-of-thyroid-dysfunction-during-covid-19-final.pdf>.