Maternal Health, Neonatology and Perinatology

REVIEW

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Overview of thyroid disorders in pregnancy

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Abstract

Thyroid disorders rank as the second most common endocrine abnormalities during pregnancy, posing significant challenges for clinical diagnosis due to overlapping symptoms with normal pregnancy. Thyroid hormones play a critical role in fetal growth and neurocognitive development, necessitating precise interpretation of maternal thyroid function tests, which differ from non-pregnant states. Proper management of thyroid dysfunction can significantly reduce morbidity in both mothers and their fetuses.

This review explores the physiological changes in thyroid function during pregnancy, the epidemiology of thyroid disorders, and current guidelines for diagnosis and management. Pregnancy induces anatomical and physiological changes in the thyroid gland, including an increase in gland size and alterations in hormone levels influenced by factors such as hCG and estrogen. These changes necessitate trimester-specific reference ranges for thyroid function tests, as the American Thyroid Association and the American College of Obstetricians and Gynecologists recommended. Hyperthyroidism, primarily caused by Graves' disease and gestational transient thyrotoxicosis, can lead to complications like preeclampsia, preterm birth, and fetal hyperthyroidism. Management includes antithyroid drugs, with careful monitoring to balance maternal and fetal risks. Hypothyroidism, including subclinical and overt forms, is predominantly due to autoimmune thyroiditis and poses risks such as spontaneous abortion, preterm delivery, and impaired neurodevelopment in offspring. The review discusses the debated benefits of levothyroxine treatment for subclinical hypothyroidism, highlighting the need for further research to establish clear guidelines.

Given the complex interplay between thyroid function and pregnancy outcomes, this comprehensive review underscores the importance of tailored, evidence-based approaches to managing thyroid disorders in pregnant women.

Keywords Thyroid dysfunction, Pregnancy

Introduction

Thyroid disorders are the second most common endocrine disorders in pregnancy. Physiologic changes in pregnancy cause anatomic and physiological changes in the thyroid gland. Symptoms of thyroid dysfunction can overlap with pregnancy symptoms, making clinical diagnosis of thyroid dysfunction challenging. Thyroid hormones are essential for the physical growth and neurocognitive development of the fetus. The laboratory interpretation of maternal thyroid function differs from that of the non-pregnant state. Proper surveillance and management of thyroid dysfunction reduces morbidity

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in both mother and fetus. The Clinical equipoise of interventional thyroid disease trial in obstetrics would be impossible as it is unethical to do a placebo-controlled trial with thyroid medication in pregnancy. This review presents the common thyroid disorders, diagnosis and management in pregnancy based on the research evidence, reviews, and clinical practice guidelines. It is essential to know the normal physiological changes in pregnancy affecting the thyroid gland and its function, as both hyperthyroidism and hypothyroidism have been associated with adverse pregnancy, fetal and neonatal outcomes. This will also help to cautiously interpret laboratory results, considering the physiological changes in pregnancy.

Thyroid hormonal metabolism in pregnant women

Pregnancy causes anatomic and physiologic changes in the thyroid gland. The gland size increases by 10–40% depending on the iodine status and vascularity of the gland [1]. The thyroid function is to produce and secrete hormones of the same chemical composition. The function does not change, but the voltage of the function changes during pregnancy. The circulating levels of total T4 increase, free T4 decreases and thyroid stimulating hormone (TSH) decreases in pregnancy due to several factors [1–3]. The blood contains the concentration of hormones in the form of the ratio between the rate of their production by the gland and the rate of their absorption by the body. In addition, T4 is converted to T3, which is the main consumed hormone. Therefore, a decrease in T4 is usually associated with excessive transformation into T3. Even though the total T3 &T concentration increases as the pregnancy advances; the free concentration of the hormones decreases because of increase in TBG concentration. Of the 3 enzymes which converts T4 to T3, type 1 iodothyronine deiodinase (D1) activity decreases in pregnancy and, as result the circulating T3 level in fetus are low. However, fetal brain level of T3 is upto 80% of adult level which helps to maintain normal brain development [4, 5].

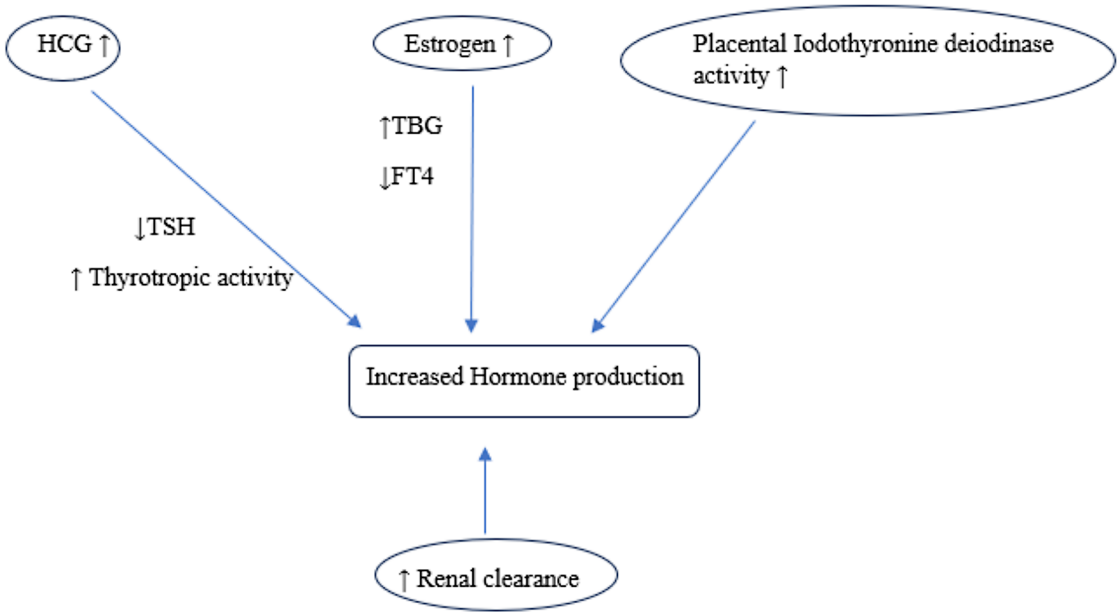
Alexander et al. (2017) wrote that Human chorionic gonadotropin (hCG), which peaks at 8–10 weeks of pregnancy, has homology with thyroxine stimulating hormone (TSH). The authors are of the opinion that hCG causes a decrease in TSH concentration and has thyrotropic activity, resulting in increased T4 levels. The lowest level of TSH occurs in the first trimester and the reference range gradually rises in the second and third trimesters [1]. Thyroid activity depends primarily on the influence of the autonomic nervous system. The dominance of the influence of the nervous system on the gland is accompanied by a smaller auxiliary influence from the pituitary gland through TSH. In addition, not all pregnant women have reduced TSH during this period. The geographic and ethnic diversity affect the measurement of TSH in pregnancy. The American Thyroid Association (ATA) and the American College of Obstetricians and Gynecologists (ACOG) recommend using population-specific, assay-specific and trimester-specific ranges for thyroid function tests in pregnant women [1]. Based on the studies in the United States and Europe, the upper reference limit of TSH is 2.5 mU/L in the first trimester and 3.0 mU/L in the second and third trimesters [1]. However, recent studies in Asia, India and the Netherlands showed only a modest reduction in the upper reference limit.

An increase in Estrogen level reduces the clearance of thyroxine-binding globulin (TBG) by the liver. So, the FT4 concentration decreases, necessitating further demand to increase thyroid hormone secretion by 50% above the preconception level. The clearance of thyroid hormone is increased by the increase in glomerular filtration rate (GFR) and renal blood flow (Fig. 1) [3]. Because the reference value of FT4 is influenced by several factors and the measurement of free T4 by a competitive immunoassay is prone to alterations, serum total T4 measurement is recommended for pregnant women [1]. Another reason for the maternal thyroid gland's increased thyroid hormone production is the increased concentration of type 3 iodothyronine deiodinases produced by the placenta to protect the fetus from the increased thyroid hormone levels. In addition, the iodine needs are increased by the increased hormone production, need for the fetus, and increased clearance [2, 3]. A study conducted in Norway showed that low iodine levels in pregnancy (< 100 µg/L) were associated with lower language skills in children up to 18 months of age [6]. The American Thyroid Association currently recommends for women planning pregnancy, pregnant, or breastfeeding to take supplements containing 150 µg of iodine a day [7]. In low-resource countries, a single annual dose of ≈ 400 mg of iodized oil for pregnant women and women of childbearing age can temporarily protect vulnerable populations [1].

Thyroid disorders in pregnancy

Thyroid hormones are involved in brain development, and the fetus depends on the maternal thyroid hormone in the first half of pregnancy. The fetal thyroid gland can synthesize the thyroid hormones from the second trimester of pregnancy [9]. T3 regulates the gene involved in cortical development and neuronal migration. Alteration in thyroid hormone in the early part of fetal brain development leads to irreversible brain damage [10].

The etiology of thyroid disease in pregnancy is multifactorial. Subclinical hypothyroidism is defined by elevated TSH with normal free T4 level. The serum level of TSH is elevated, and free T4 is decreased in overt



HCG: Human chorionic gonadotrophin; TBG: Thyroid binding globulin; FT4: Free T4; TSH: Thyroxine stimulating hormone

Fig. 1 A hypothetical representation of thyroid function in pregnancy

hypothyroidism. Similarly, subclinical hyperthyroidism is diagnosed by low serum TSH and normal free T4 level and overt in hyperthyroidism, the serum level of free T4 is elevated with low TSH level [11].

The predominant type of thyroid disease in pregnant women is autoimmune thyroid disorders such as Hashimoto's thyroiditis and Graves' disease [9]. Overt hyperthyroidism complicates in 0.2–0.7% of pregnancies, subclinical hyperthyroidism in 0.8–1.7% of pregnant women, overt hypothyroidism occurs in 0.2–0.6% of pregnant women and subclinical hypothyroidism occurs in 3.5-18% of all pregnancies, depending on the definition used [12, 13]. A study from Denmark reported 12.5% abnormal thyroid function from pregnant women enrolled in the Danish National Birth Cohort, 1997–2003 [9]. The American Thyroid Association (ATA) guidelines recommend using fixed upper limits of 2.5 mU/l or 3.0 mU/l for the first and second or third trimesters, respectively [1]. Studies have shown that the prevalence of subclinical hypothyroidism was lower when population-based trimester-specific reference values were used [14, 15]. The prevalence of thyroid peroxidase antibody (TPO Ab) positivity in the first trimester ranges from 5 to 15%, varying with ethnicity. The prevalence ranges from 23 to 31% in those women with recurrent pregnancy losses [1, 8].

Hyperthyroidism in pregnancy

The causes of hyperthyroidism in pregnancy include Graves' disease and gestational transient thyrotoxicosis (GTT), toxic multinodular goiter or solitary toxic thyroid adenoma, subacute de Quervain's thyroiditis, acute thyroiditis, factitious intake of thyroid hormone, TSH-producing pituitary adenoma and struma ovarii (a rare ovarian tumor containing thyroid tissue) [16, 17]. A recent meta-analysis demonstrated that Subclinical hyperthyroidism in pregnancy is not related to adverse maternal or fetal outcomes [18].

Gestational transient thyrotoxicosis

GTT occurs due to elevated thyroid hormone from increasing human chorionic gonadotropin (hCG) levels. Prevalence varies from 0.3 to 11% depending on geographical locations. GTT is more common in multiple pregnancies and hydatidiform mole because of the marked elevation of hCG. GTT is rarely due to a heterozygous TSH receptor (TSHR) gene mutation. Hyperthyroidism is usually mild and transient. Symptoms typically develop in 4–9 weeks, with normalization of thyroid hormones by 14 to 20 weeks of gestation. Only a few patients are symptomatic, which includes nausea, vomiting, and hyperemesis gravidarum. The others may present with palpitations, tremors, anxiety, nervousness, heat intolerance, and weight loss. The diagnosis is confirmed by low to undetectable TSH, elevated FT4 level, and normal or slightly elevated triiodothyronine (T3) level due to enhanced peripheral conversion of FT4 to reverse

triiodothyronine (rT3) [15, 16]. Decreased FT3/FT4 ratio distinguishes GTT from Graves' disease. Infants born to mothers with GTT and severe hyperemesis were reported to have low birth weight compared to infants born to unaffected mothers. Treatment is usually not indicated because of its transient nature. Propranolol can reduce the symptoms of thyrotoxicosis and hyperemesis in a minority of patients with severe symptoms.

Grave's disease

The most common cause of hyperthyroidism in pregnancy is due to Graves' disease, which is seen in 0.2% of pregnant women. Graves' disease is provoked by a more active influence of the autonomic nervous system, and the role of the immune system is secondary. And the severity of hyperthyroidism in Graves' disease can be different (minor, moderate or significant). This also applies to pregnant women who have an overstrained autonomic nervous system [19, 20]. The thyrotoxicosis transiently worsens in the first trimester, followed by improvement in the 2nd and 3rd semesters and rebound worsening in the postpartum period. These variations in clinical symptoms are due to the higher levels of antibodies, immune tolerance in pregnancy by specific T-cell subsets (regulatory T [TREG] cells and higher levels of hCG in the first trimester [17, 21, 22].

Clinical effects of hyperthyroidism in pregnant women, fetuses, and neonates

Nonspecific symptoms such as anxiety, palpitation, sleeplessness, and fatigue are common in pregnancy and hyperthyroidism. However, if combined symptoms, such as weight loss or failure to gain weight, thyroid swelling, and ocular symptoms, then the diagnosis of hyperthyroidism is more likely.

Pregnancy-related complications of hyperthyroidism include preeclampsia (3.9-fold higher risk), fetal growth restriction (2.2-fold higher risk), preterm birth (1.7-fold higher), induction of labor (3.6-fold higher) and higher risk of miscarriages, stillbirth (5.6%) or fetal death [23–25]. Thyroid storm is an infrequent life-threatening complication and is characterized by altered mental status, hyperthermia, widened pulse pressure, tachycardia, left ventricular dysfunction, and multi-organ failure. Another severe complication is heart failure, which occurs in 10% of untreated severe hyperthyroid pregnant women.

Fetal hyperthyroidism is rare and occurs in 1% of neonates born to mothers with Graves disease [26, 27]. Fetal hyperthyroidism develops because of the transfer of maternal TRAbs, stimulating epithelial cells in the fetal thyroid gland [26]. It may occur in the fetus and neonates of mothers previously treated for Graves' disease in whom circulating TRAbs persist. Fetal hyperthyroidism, which develops in the second trimester of pregnancy, is characterized by fetal tachycardia, heart failure, non-immune hydrops, fetal goiter, accelerated bone maturation, and IUGR. Fetal ultrasonography has been proven sensitive and specific for detecting intrauterine thyroid dysfunction. A fourfold level of TRAb levels above the reference range predicted neonatal hyperthyroidism with a positive predictive value of 40% [27]. Neonatal manifestations include hyperthermia, irritability, diarrhea, feeding difficulties, poor weight gain, periorbital edema, retraction of the eyelid, small anterior fontanel, tachycardia, heart failure, hypertension, hepatomegaly, splenomegaly, cholestasis, thrombocytopenia, and hyperviscosity. Neonatal hyperthyroidism is usually transient, but few patients need treatment with beta blockers and antithyroid drugs.

Diagnosis

The diagnosis of Graves' disease is by detecting suppressed TSH levels along with elevated thyroid hormones. Interpretation of thyroid function tests depends on several factors, as mentioned before. The tests should be done when the pregnancy is planned or as soon as the pregnancy is diagnosed. Measurement of TRAbs helps distinguish gestational thyrotoxicosis and Graves' disease and assesses the risk of fetal hyperthyroidism [24, 28]. Repeating TRAbs every two months helps assess the disease activity. Ultrasound of fetal thyroid gland scan by an experienced ultra-sonographer should be performed 20 weeks onwards to detect fetal thyroid dysfunction [28]. Assessment of fetal heart rate and fetal bone maturation also guides the diagnosis of fetal hyperthyroidism. Determination of elevated levels of TRAb levels in cord blood helps identify neonates with autoimmune hyperthyroidism.

Treatment of hyperthyroidism in pregnancy and postpartum

Commonly used antithyroid drugs (ATD), methimazole (MMI), and propylthiouracil (PTU) act by inhibiting utilization of iodine by the thyroid gland, thereby decreasing the thyroid hormone synthesis. Propylthiouracil also inhibits mono-deiodination of T4 to T3 [24]. These drugs might have immunosuppressive effects, leading to a decrease in the level of TRAb. The dose ranges from 100 to 300 mg daily of PTU and 5–30 mg daily of MMU with titration of dose based on the response. When considering drug treatment, several factors should be considered, such as the severity of hyperthyroidism and the adverse effects of the drug on the mother and the fetus. Methimazole, being free in serum, crosses the placenta. Often, PTU is recommended in the first trimester and transition to MMI in the second trimester [1]. Rare reported teratogenic effects of MMI include esophageal or choanal atresia, omphalocele, aplasia cutis congenita,

omphalomesenteric duct abnormalities, and nipple and eye malformations. PTU exposure, even though rare, is associated with milder congenital disabilities such as preauricular sinus/ fistula or urinary tract anomalies [17, 28]. Adverse maternal effects of ATDs include pruritic rash, gastrointestinal upset, or fever (5–10%), antineutrophil cytoplasmic antibody-positive vasculitis, migratory polyarthritis, lupus-like symptoms, agranulocytosis (0.3–0.5%) and hepatotoxicity. Hepatotoxicity from MMI is cholestatic, and PTU can cause hepatocellular damage. Thyroid function tests should be done two weeks after initiating, transitioning, or adjusting doses of medications to maintain free T4 in the upper normal range [17].

The other treatment options include thyroidectomy, potassium iodide, and beta blockers. Thyroidectomy can be done in the second trimester if the symptoms are uncontrolled, even with a higher dose of medicine, or if there are compressive symptoms from the enlarged gland. Complications include abortion, early or threatened labor, fetal distress, intrauterine death, or stillbirth [22]. Beta-blockers may be used to alleviate the symptoms of hypermetabolism but should be discontinued, when possible, because of the adverse effects such as neonatal bradycardia and neonatal hypoglycemia [16, 17]. Treatment with potassium iodide has not been studied extensively and is not recommended during pregnancy as it has been associated with fetal hypothyroidism and goiter. Radioactive iodine treatment is contraindicated in pregnancy because of its teratogenic side effects.

Hypothyroidism in pregnancy

Hypothyroidism in pregnancy can be subclinical hypothyroidism, overt hypothyroidism, or isolated hypothyroxinemia. Subclinical hypothyroidism is more common than overt hypothyroidism. The most common cause of overt hypothyroidism in pregnancy in iodine-sufficient areas is due to Hashimoto's thyroiditis. Other causes are hypothyroidism following surgery for multinodular goiter, Graves' disease or thyroid cancer, following radioactive iodine treatment of Graves' disease, overtreatment of hyperthyroidism with ATDs, medications that alter the absorption or metabolism of LT4 and central defects that inhibit the hypothalamic-pituitary-thyroid axis [29].

Subclinical hypothyroidism (SCH)

Subclinical hypothyroidism is diagnosed based on elevated TSH concentration and normal free thyroxine level. Risk factors for SCH include iodine deficiency, personal/family history of thyroid disease, positive thyroid antibodies, type 1 diabetes, autoimmune disorders, radiation exposure to head and neck area, and history of amiodarone and lithium use [30].

Maternal outcome of subclinical hypothyroidism

The studies reported the adverse events associated with SCH are of poor quality. The reported prevalence of subclinical hypothyroidism in women with recurrent pregnancy loss is 12.9%. Based on current observational studies, there is no association between subclinical hypothyroidism and recurrent pregnancy loss, defined by nonconsecutive pregnancy losses. However, an association may exist between consecutive recurrent pregnancy loss and subclinical hypothyroidism [31]. SCH is associated with placental abruption (RR 2.14 [CI 1.23–3.70]), premature rupture of membranes (RR 1.43 [CI 1.04–1.95]), and neonatal death (RR 2.58 [CI 1.41–4.73]) [32]. A systematic review of 52 cohorts involving 39862 women showed that subclinical hypothyroidism was associated with a higher risk of preeclampsia (3.6% vs. 2.1%; OR, 1.53 [95%CI, 1.09 to 2.15]) compared to euthyroidism [33]. A meta-analysis and systematic review of 19 cohort studies including 47045 women showed that the risk of preterm birth was higher for women with subclinical hypothyroidism than euthyroid women (6.1%vs 5.0%, respectively; absolute risk difference, 1.4% [95%CI, 0-3.2%] [31]. Even though some studies have correlated adverse pregnancy outcomes with SCH, more research is necessary to elucidate the causation and/or benefit of treatment.

Fetal/Neonatal/Childhood outcome of SCH

Multiple studies have shown that thyroid hormones regulate fetal growth by facilitating placentation, fetal glucose and oxygen consumption, and other co-factors directly affecting skeletal growth, tissue differentiation, and accretion. Maternal SCH is associated with a higher risk of SGA compared to euthyroidism and lower mean birth weight [35]. In a retrospective study involving 8,413 pregnant women, infants of women with subclinical hypothyroidism had increased risks of respiratory distress syndrome (RR 2.8, 95% CI 1.01–7.78) compared with the dangers in euthyroid women [36]. Systematic review and meta-analyses of 37 observational studies and 2 RCT showed that maternal subclinical hypothyroidism and hypothyroxinemia are associated with indicators of intellectual disability in offspring (odds ratio [OR] 2.14, 95% confidence interval [CI] 1.20 to 3.83, $P=.01$, and OR 1.63, 95% CI 1.03 to 2.56, $P=.04$, respectively). Maternal subclinical hypothyroidism and hypothyroxinemia were not associated with attention deficit hyperactivity disorder, and their effect on the risk of autism in offspring was unclear. Meta-analysis of RCTs showed no evidence that levothyroxine treatment for maternal hypothyroxinemia or subclinical hypothyroidism reduces the incidence of low intelligence quotient in offspring [37]. A prospective study from the Netherlands showed that low and high

maternal thyroid function is associated with smaller total grey matter and cortical volume [38].

As a result of the positive association of subclinical hypothyroidism with adverse maternal, fetal, and neonatal outcomes, many health organizations, including the 2017 American Thyroid Association guideline, recommend levothyroxine treatment for women with subclinical hypothyroidism diagnosed in pregnancy. In a retrospective cohort study of 5405 pregnant women with subclinical hypothyroidism, thyroid hormone treatment was associated with lower odds of pregnancy loss but higher odds of preterm delivery (1.60, 1.14 to 2.24), gestational diabetes (1.37, 1.05 to 1.79), and preeclampsia (1.61, 1.10 to 2.37) [39]. A systematic review of 3 trials of low to unclear risk of bias with 1837 participants found no evidence of the benefit of levothyroxine therapy on obstetrical, neonatal, childhood IQ, or neurodevelopmental outcomes [40]. So, the current evidence is insufficient to show that thyroid hormone treatment improves clinical outcomes in pregnant women with subclinical hypothyroidism.

Overt hypothyroidism

Hypothyroidism may present with nonspecific symptoms and signs that may be indistinguishable from common signs or symptoms of pregnancy, such as fatigue, constipation, cold intolerance, muscle cramps, and weight gain. Other features are edema, dry skin, hair loss, goiter and a prolonged relaxation phase of deep tendon reflexes.

Maternal complications

Maternal adverse consequences of overt hypothyroidism include spontaneous abortion, fetal death, gestational hypertension, preeclampsia, anemia, placental abruption, cesarean section, preterm delivery, and postpartum hemorrhage [41]. A French cohort study showed that pre-pregnancy thyroid diseases were associated with gestational diabetes (odds ratio [OR] = 1.58 [95% confidence interval [CI]1.08, 2.30]), infertility treatment (OR = 1.57 [95% CI 1.07, 2.31]) and premature rupture of membranes (OR = 1.51 [95% CI 1.01, 2.25]) [42].

Neonatal/Childhood outcome

The immediate neonatal and long-term adverse outcomes are rare and occur mainly in poorly controlled maternal hypothyroidism. In a large, nationwide cohort study from the United States, maternal hypothyroidism was associated with increased odds of respiratory distress syndrome, apnea, transient tachypnea of the newborn, large for gestational age infants, lower intelligence quotient, and poorer motor development in children [43]. Other associations reported include delays in the development of expressive language, decrement of orientation, vision abnormalities, and behavioral changes in children born to women with hypothyroidism in pregnancy. An RCT involving 21,846 women showed that the mean IQ scores were not different in women treated with levothyroxine treatment at 13 weeks compared to control groups, and the proportions of children with an IQ of less than 85 were 12.1% in the screening group and 14.1% in the control group [44]. A possible explanation for the study's negative results could be because of late screening and treatment after the first trimester. A meta-analysis of individual participant data from 9036 mother-child pairs from three prospective population-based birth cohorts showed that FT4,2.5th percentile was associated with a 3.9-point (95% CI, 25.7 to 22.2) lower nonverbal IQ and a 2.1-point (95%CI,24.0 to20.1) lower verbal IQ [45].

Thyroid autoimmunity

Thyroid autoimmunity is the most common autoimmune disease of the reproductive age group. Autoimmunity can occur in the presence or absence of thyroid dysfunction. Thyroid peroxidase antibodies (TPOAbs), thyroglobulin antibodies (TgAbs), and TSH receptor antibodies (TRAbs) are the antithyroid antibodies (ATAs) seen in autoimmune thyroid disease (ATD). TRAbs are divided into TSHR-stimulating antibodies (TSAbs), TSHR-blocking antibodies (TBAbs), and neutral TRAbs (N-TRAbs) [46]. The prevalence of TPOAbs and TgAbs in pregnant women is 5–14% and 3–18%, respectively [47]. These antibodies decline in the second trimester, followed by an increase postpartum. Thyroid autoimmunity decreases the functional capacity of the thyroid gland, which can lead to hypothyroidism. Antibodies to thyroid peroxidase and thyroglobulin are increased in both Graves disease and Hypothyroidism and both conditions have similar ultrasound picture [48]. High concentrations of hCG in early pregnancy stimulate the thyroid, leading to a net increase in thyroid hormones.

Studies evaluating thyroid antibody positivity and infertility showed mixed results. A recent systematic review and meta-analysis showed a significantly higher risk of diminished ovarian reserve in women with Hashimoto's thyroiditis [49]. They did not perform a sub-analysis in a group of euthyroid women. A recent case-control study of 4,302 euthyroid women showed that thyroid autoimmunity was associated with premature ovarian insufficiency in the group with TSH > 2.5 μIU/ml but not in those with TSH ≤ 2.5 μIU/ml [50].

In a systematic review involving 46,528 pregnant women, TPO antibody positivity was not associated with gestational hypertension or preeclampsia [33].

One systematic review and meta-analysis showed that the odds of miscarriage more than tripled (12126 women) and that of preterm birth doubled (12566) in women with thyroid autoantibodies [51]. TPOAb-positive women with an adequate expected thyroidal response to hCG did

not have a higher risk of premature delivery [52]. A systematic review involving 47,045 pregnant women showed a higher risk of preterm delivery for TPO antibody–positive women and a thyrotropin concentration higher than 4.0 mIU/L [34]. Levothyroxine treatment reduced preterm birth only if the thyrotropin concentration was higher than 4.0 mIU/L.

The 2017 American Thyroid Association pregnancy guidelines strongly recommend levothyroxine for women with thyroid autoimmunity and a thyroid-stimulated hormone above the pregnancy-specific reference range. They may be considered for euthyroid women with positive TPOAb and a history of pregnancy loss [1]. However, a recent systematic review and meta-analysis of randomized controlled trials of f 2263 women by Lau L et al. showed that there is a lack of evidence of benefit for levothyroxine use among pregnant women or women planning conception with thyroid autoimmunity [8].

Thyroid autoimmunity is an ever-evolving subject and therefore it will not be surprising if there are paradigm shift in our understanding of these diseases in the near future.

Iodine deficiency in pregnancy

Globally, iodine deficiency is the most common cause of hypothyroidism. In pregnancy, iodine intake should increase by 50% due to a physiologic increase in thyroid hormone, increased urinary iodine losses, and transplacental transport of iodine for fetal thyroid hormone synthesis [53]. Severe iodine deficiency in pregnancy increases the risk of miscarriage, premature birth, stillbirth, maternal and fetal goiter, cretinism in neonates, impaired mental function, deaf mutism, poor school performance, reduced intellectual ability, and stunted growth [11]. Observational studies have shown an inconsistent association between mild to moderate iodine deficiency and miscarriage, preterm birth, preeclampsia, low birth weight, and neonatal intensive care unit admission. The impact of mild to moderate iodine deficiency on child neurodevelopment is uncertain [54]. Currently, the ATA, the Endocrine Society, the US Teratology Society, the American Academy of Pediatrics, and the ETA recommend that women who are planning to be pregnant, are pregnant, or are breastfeeding should take a daily oral supplement containing 150 μg of iodine. The positive effect of iodine supplementation is more evident in moderately iodine-deficient areas than in mildly iodine-deficient areas [55].

Postpartum thyroiditis (PPT)

Thyroid dysfunction within the first year postpartum is usually seen in those patients without a prior history of thyroid nodule or TSH receptor antibodies [56]. It is an autoimmune process resulting from the increased release of thyroid antibodies after delivery following immune tolerance induced by pregnancy. The patients undergo a phase of transient thyrotoxic state lasting for 2–3 months followed by hypothyroidism lasting for 3–6 months, and the majority of them become euthyroid within a year [11, 56]. The hypothyroid phase may persist in 20–30% of cases. PPT can be easily misdiagnosed as postpartum depression. It may interfere with lactation. A high T4:T3 ratio can help to distinguish PPT from Graves' disease. A radioactive iodine uptake test can also help distinguish PPT from Graves' disease if needed. ATD is not useful, and beta-blockers may be used if hyperthyroid symptoms are bothersome. The symptomatic hypothyroid phase is treated with levothyroxine, which can be tapered and stopped in 6–12 months.

Screening for hypothyroidism

ACOG and the American Society of Reproductive Medicine do not recommend universal screening for thyroid disease in pregnant women. A prospective randomized trial in Italy involving 4562 women did not find adverse outcomes when universal screening was compared with 'case finding '(identify and test for high-risk women) [57]. Universal screening would uncover more cases of subclinical hypothyroidism for which the evidence for the benefits of treatment is insufficient [11]. There is an ongoing discussion on TSH and TPO antibody cut-off value for treatment consideration in pregnant women. Based on current evidence, targeted screening of pregnant women at increased risk for thyroid dysfunction is advisable. The risk factors include women with a family history of autoimmune thyroid disease or hypothyroidism, goiter, thyroid antibodies, symptoms or clinical signs suggestive of thyroid hypofunction, type 1 DM or other autoimmune disorders, history of infertility, prior history of miscarriage or preterm delivery, prior therapeutic head or neck irradiation, prior thyroid surgery, those who are currently receiving levothyroxine replacement and women living in a region with presumed iodine deficiency [58].

Thyroid nodule and cancer in pregnancy

Thyroid nodule

Prevalence of thyroid nodule ranges from 3 to 30% depending on iodine status. Pregnancy has been associated with the enlargement of existing thyroid nodules and the appearance of new nodules. Increasing size is due to the thyrotrophic effects of hCG and the TSH stimulation resulting from the depletion of iodine stores. Whether it is related to increased incidence of malignancy is uncertain. Initial evaluation includes serum TSH and thyroid ultrasonogram. A depressed level of TSH indicates hyperfunctioning nodules [59]. Fine needle aspiration cytology is recommended if the nodule size is more than

1 cm, the ultrasonographic features suggest malignancy, or if there is a strong family history of malignancy. Radionuclide iodine scintigraphy is contraindicated in pregnancy as maternal radionuclides can potentially result in fetal irradiation. Benign nodules need no special monitoring and are managed similarly to the general population. Surgery is indicated if there is a cytological change or compressive symptoms [60].

Thyroid cancer

Thyroid cancer is the second most common cancer in the perinatal period. There is only limited data on the impact of pregnancy on the prognosis and progression of thyroid cancer. It is advisable to delay surgery until postpartum as there was consensus among all studies that delaying surgery did not affect long-term survival or change in tumor volume. If indicated, surgery can be done in the second trimester. Radioactive ablation should be postponed until post-partum [11, 59, 60]. Mother should be counseled to stop breastfeeding 6 weeks to 3 months before radioiodine as the lactating mammary gland takes up iodine.

Conclusions

Thyroid dysfunction is common in pregnancy. Due to physiological changes in pregnancy, trimester-specific and population-specific reference values should be adopted when interpreting the thyroid function. The evidence is unclear about the effect of thyroxine treatment in subclinical hypothyroidism on pregnancy outcomes like pregnancy loss and preterm labor. There are reports of adverse events associated with thyroxine replacement in women with subclinical hypothyroidism. It is unclear whether thyroid antibodies are associated with infertility and assisted reproductive technology outcomes. Low-dose thyroxine can be given to those women. Even though iodine supplementation in moderate to severe iodine-deficient areas is beneficial, the detrimental effects of excess iodine on pregnancy and neurodevelopmental outcomes should be considered before prescribing iodine to women in iodine-sufficient or mildly deficient regions. Future studies are expected to reveal a better understanding of the management of thyroid dysfunction in pregnancy.

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