Archives of Gynecology and Obstetrics (2019) 299:327–338
https://doi.org/10.1007/s00404-018-5018-8

REVIEW

Thyroid function and thyroid disorders during pregnancy: a review and care pathway

Alessandro P. Delitala[1] · Giampiero Capobianco[2] · Pier Luigi Cherchi[2] · Salvatore Dessole[2] · Giuseppe Delitala[2]

Received: 19 February 2018 / Accepted: 12 December 2018 / Published online: 19 December 2018

Abstract

Purpose To review the literature on thyroid function and thyroid disorders during pregnancy.

Methods A detailed literature research on MEDLINE, Cochrane library, EMBASE, NLH, ClinicalTrials.gov, and Google Scholar databases was done up to January 2018 with restriction to English language about articles regarding thyroid diseases and pregnancy.

Results Thyroid hormone deficiencies are known to be detrimental for the development of the fetus. In particular, the function of the central nervous system might be impaired, causing low intelligence quotient, and mental retardation. Overt and subclinical dysfunctions of the thyroid disease should be treated appropriately in pregnancy, aiming to maintain euthyroidism. Thyroxine (T4) replacement therapy should reduce thyrotropin (TSH) concentration to the recently suggested fixed upper limits of 2.5 mU/l (first and second trimester) and 3.0 mU/l (third trimester). Overt hyperthyroidism during pregnancy is relatively uncommon but needs prompt treatment due to the increased risk of preterm delivery, congenital malformations, and fetal death. The use of antithyroid drug (methimazole, propylthiouracil, carbimazole) is the first choice for treating overt hyperthyroidism, although they are not free of side effects. Subclinical hyperthyroidism tends to be asymptomatic and no pharmacological treatment is usually needed. Gestational transient hyperthyroidism is a self-limited non-autoimmune form of hyperthyroidism with negative antibody against TSH receptors, that is related to hCG-induced thyroid hormone secretion. The vast majority of these patients does not require antithyroid therapy, although administration of low doses of β-blocker may by useful in very symptomatic patients.

Conclusions Normal maternal thyroid function is essential in pregnancy to avoid adverse maternal and fetal outcomes.

Keywords Thyroid disease · Pregnancy · Hypothyroidism · Hyperthyroidism · Adverse fetal outcome

Introduction

Thyroid disorders are common in the general population [1] and have been associated with cardiovascular disease [2, 3], metabolic syndrome [4], and mood disorders [5, 6]. Normal thyroid function is essential in pregnancy to avoid complications in gestation and to ensure delivery of a normal baby. Thyroid diseases, after diabetes, are the commonest endocrine disorders during pregnancy. Low thyroid hormone levels during pregnancy can have detrimental effect on the development of the fetal central nervous system, and predispose to preterm delivery (RR 1.35) and increased risk of miscarriage (RR 1.90) [7].

Although hyperthyroidism in pregnancy is much less common than hypothyroidism, maternal, fetal and neonatal complications such as eclampsia, small for gestational age, prematurity and low birth weight are significantly increased in uncontrolled disease [8, 9]. A correct management of these thyroid disorders should focus on the mother as well as the fetus and should require a multidisciplinary approach to avoid maternal, fetal, and neonatal complications. Pharmacological therapy should be tailored to single pregnant woman to keep thyroid hormone levels within the pregnant reference range.

The aim of this review is to discuss what is known about the interplay between thyroid diseases and pregnancy and the available evidences on the management of the different

✉ Alessandro P. Delitala
aledelitala@tiscali.it

[1] Azienda Ospedaliero-Universitaria Di Sassari, Clinica Medica, Viale San Pietro 8, 07100 Sassari, Italy

[2] Department of Medical, Surgical and Experimental Sciences, University of Sassari, 07100 Sassari, Italy

thyroid alterations in pregnancy as well as on existing guidelines on this field for a more rational management of these disorders during pregnancy.

Methods of search strategy

A detailed literature research on MEDLINE, Cochrane library, EMBASE, NLH, ClinicalTrials.gov, and Google Scholar databases was done up to January 2018 with restriction to English language about articles regarding thyroid disorders and pregnancy and most recent treatment options. The keywords used for this review were: "subclinical hypothyroidism", "subclinical hyperthyroidism", "hypothyroidism", "hyperthyroidism", "thyroid disorders", "pregnancy", and "fetal development". Original articles, reviews, and meta-analysis were included. Three authors (A. D., G. C. and G. D.) selected the studies independently on the basis of the inclusion criteria. Disagreements among authors as to the studies to include were solved by discussion. In cases of duplication, the study with the most recent data was included. In case of cohort studies with multiple publications, the last dataset on efficacy was used.

Maternal thyroid hormones across pregnancy

The main thyroid hormones in humans are thyroxine (T4) and 3,5,3′-triiodo-L-thyronine (T3). The synthesis and secretion of these hormones are finely regulated by the thyroid-stimulating hormone (TSH) axis whose activity is negatively regulated by thyroid hormones. The most abundantly thyroid hormone secreted by the thyroid gland is T4 whereas about 10% of circulating T3 is directly produced by the thyroid. T4 is considered to be a reservoir for the production of T3, since the majority of T3, which is considered to be the biological active form of thyroid hormones, is produced by T4 conversion by type 1 iodothyronine deiodinases (D), which is distributed in every all tissues [10]. Both deiodinase 2 (D2) and deiodinase 3 (D3) are expressed in the brain. D3 inactivates T4 by converting it into reverse T3, a metabolically inactive compound, and converts T3 to diiodothyronine (T2) whereas D2 functions to convert T4–T3. D2 is primarily expressed in glial cells of various regions of the central nervous system (CNS) and plays an important role in its development and function. In particular, type 3 deiodinase is expressed in high amounts in the placenta, where it protects the fetus from toxic levels of thyroid hormones by converting T4 to biologically inactive reverse T3 in the periphery [11, 12]. One of the most important physiological mechanisms to keep the fetus euthyroid is the presence of uteroplacental barrier, which transfers thyroid hormone from the mother to the fetus [13].

The complex actions of thyroid hormones are initiated by the intracellular binding of T3 to nuclear receptor where they cause alterations in gene expression. This nuclear genomic effect of thyroid hormones is exerted by either inducing or repressing the expression of target genes [14]. Thyroid hormones also affect cell function through a non-genomic action, which is independent of nuclear receptor. This action is exerted at the cellular membrane with the generation of second intracellular second messengers, such as calcium and cyclic adenosine monophosphate (cAMP) [14]. Both mechanisms are physiologically important in regulating cell differentiation and function. Thus, thyroid hormones play an important role in the regulation of many physiologic processes such as heart rate [15], blood pressure and arterial stiffening [16, 17], lipid metabolism and atherosclerosis [18–21], and neural development [22].

Various physiological changes that occur across the normal pregnancy increase the demands of the maternal thyroid gland [23]. In the pregnant women there is an increase in T4 and T3 production in response to the estrogen-stimulated rise in the thyroid hormone transport protein, thyroxine-binding globulin (TBG). This thyroid hormone increases plateau at 12–14 weeks of pregnancy until a new steady state is reached [23]. Also in the first trimester, there is a transient inhibition of TSH that coincides with peak human chorionic gonadotropin (hCG) concentration [24]. Due to the structural homology between TSH and hCG molecule, hCG exerts a stimulatory effect on thyroid hormone synthesis and secretion by binding to the TSH receptor on thyrocytes, which results in lowering TSH levels during the first trimester of pregnancy via the negative feed-back system [23]. Starting from the early weeks of gestation, there is a progressive decrease of free-T4 during pregnancy (Fig. 1). Moreover, a large plasma volume, and thus altered distribution of thyroid hormones, increased thyroid hormone metabolism, together with increased renal clearance of iodide are responsible for higher thyroid hormone requirements in pregnancy. Given that the fetus thyroid gland starts function after the first trimester, this hormonal milieu ensures a proper amount of thyroid hormones delivery to the fetus at a critical time of neurological development. In fact, the most important maternal thyroid hormone for the fetus is T4, because T4 crosses the placental barrier and achieves the fetus. The consequent fetal consumption of maternal thyroid hormone, together with increasing concentration of TBG, increasing urinary iodide clearance and increasing thyroid hormone degradation by placental D3, necessitates an increase in maternal thyroid hormone secretion to ensure adequate fetal thyroid hormone availability. Such a new physiological demand requires an adequate iodine intake by pregnant women that when not fulfilled can alter thyroid gland function, causing thyroid hormone deficiency.

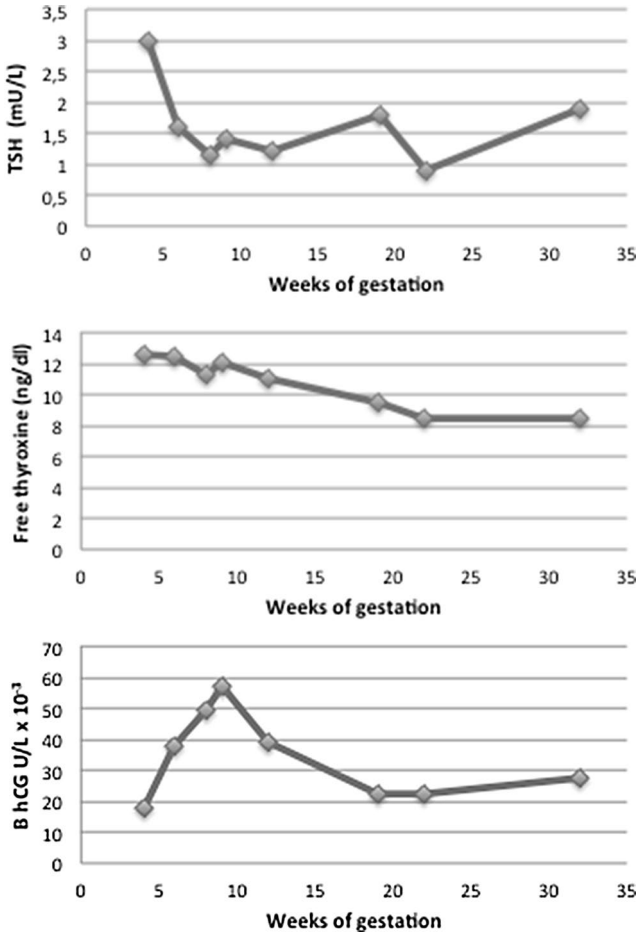

Fig. 1 Variations of thyroid hormones and β hCG across pregnancy. Modified from Glinoer [23]

Thyroid function-dependent fetal development

During embryogenesis, thyroid hormones are of critical importance in the normal development of the fetus and of the human central nervous system [25]. How abnormal thyroid hormone levels during a pregnancy may influence the fetal development has been studied for decades [26]. Although the fetal thyroid in humans can synthesize thyroid hormones by the 10–12 weeks of gestation [27], it is not until midgestation that important amounts of thyroid hormone are produced by the fetal thyroid gland (Fig. 2). Hence, maternal hypothyroxinemia during the first trimester of gestation can have deleterious effects on fetal development, which is largely dependent on maternal T4.

The adverse effects of abnormal maternal thyroid function in pregnancy have been well documented in states of severe iodine deficiency [28], where neurological and myxedematous cretinism are disorders of profound mental and physical disability. Thyroid hormones influence brain development through modifications in the expression of a host of genes that are involved in coordinated and timely regulation of many different development processes like cell proliferation, neurogenesis, cell migration differentiation, synaptogenesis and myelinisation, as well as modifications in the neurochemical environment in the brain [29].

The functional consequence of maternal dysfunction, particularly during the first trimester of pregnancy, on the fetal brain development in humans has mainly been studied from neuropsychological testing of altered offspring neurodevelopment. Subtle alterations in cognitive function, intelligence quotient, developmental delays in infancy, emotional problems, or hyperactivity/inattention have been described, although not univocally reported [30–40]. An increased risk for the offspring to develop autism has also been associated with maternal hypothyroxinemia [41]. More recently

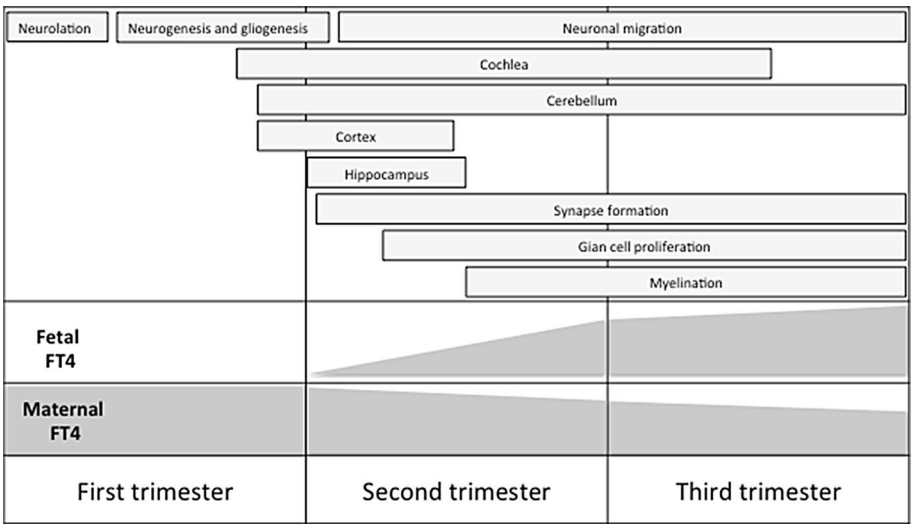

Fig. 2 Development of central nervous system and thyroid function

morphological changes in the brain of children exposed to abnormal thyroid function in pregnancy have been evaluated with magnetic resonance scans. Some studies reported abnormal cortical morphology with smaller volume of the hippocampus and abnormal development of corpus callosum [42–44], although no association between maternal hypothyroxinemia and offspring brain morphology was found in another report [36].

Collectively, the data clearly demonstrated that the maternal low T4 levels during the first trimester of pregnancy are likely correlated with the risk of developing adverse fetal outcomes. Early diagnosis and correct management of thyroid dysfunction in pregnancy is essential to avoid adverse maternal and fetal complications.

Iodine during pregnancy

In early gestation, maternal thyroid hormone production normally increases by approximately 50% in response to the increased metabolic demands of the fetal–maternal unit. This increased thyroid hormone demand necessarily requires an adequate iodine supply that is mainly obtained from the diet or with supplemental iodine. Moreover, when fetal thyroid hormone production physiologically increases during the second half of pregnancy, there is an additional maternal iodine requirement because iodine readily crosses the placental barrier.

Iodide is rapidly and fully absorbed through the stomach and duodenum and then transported through the circulation where it is taken up by the thyroid in different amounts, depending on the functional state of the thyroid and the iodine supply, or it is renally excreted. The latter represents the primary route of iodine excretion, which accounts for more than 90% of ingested iodine [45]. Iodide metabolism rapidly changes during early pregnancy, because the glomerular filtration rate of iodide increases by 30–0% [46], thereby further decreasing the circulating pool of plasma iodine [47, 48]. Iodine nutrition in pregnancy and lactation is reflected by a decline in urinary iodine excretion. The inability to compensate for the augmented iodine demand in pregnancy causes the development of maternal goiter due to TSH stimulation. For these reasons, dietary iodine requirements are higher in pregnant women than in non-pregnant individuals.

Insufficient iodide levels during pregnancy result in severe neurologic and psychological deficit in children as well as endemic goiter, intrauterine growth retardation (IUGR), increased pregnancy loss and infant mortality [48–50]. Adequate urinary iodine concentrations in pregnancy are>150 mcg/L while daily dietary iodine intake should be >200 µg [51]. The World Health Organization recommends that pregnant (and lactating) women should have an iodine intake of 250 mcg per day, which is 100 mcg above that recommended for non-pregnant women. In iodine-deficient areas, maternal iodine supplementation with iodized salt have demonstrated reduction in the rates of fetal death, endemic cretinism, and decreased thyroid volume as well as improvements in infants' neurocognitive functions [48].

Thyroid disease in pregnancy. Diagnosis and management of hypothyroidism, subclinical hypothyroidism, gestational hypothyroxinemia.

Hypothyroidism

The prevalence of overt maternal hypothyroidism (elevated TSH concentration of 10 mU/l or greater, with free T4 below the reference value) [52] in pregnancy is estimated to be between 0.3% and 1.5 in different studies [24, 34, 53–55]. Its commonest cause is autoimmune thyroiditis, but is often pre-existent, previous surgery, or radioactive iodine treatment for thyroid cancer, goiter or hyperthyroidism being the most frequent clinical conditions. Untreated hypothyroidism has been associated with an increased incidence of adverse fetal and maternal complications in pregnant women. These include preterm birth, perinatal death, pre-eclampsia and placental abruption [56]. Adverse effects on neuropsychological development or intelligence quotient have also been associated with untreated hypothyroidism [57, 58]. Since the placental transfer of maternal T4 is crucial for optimal fetal development, levo-thyroxine therapy should be initiated as soon as possible targeting TSH level to the recommended values, particularly during the first trimester of pregnancy [59]. The levo-thyroxine requirements usually plateau from 16–18 weeks of gestation until delivery [58]. Euthyroid patients with pre-existing hypothyroidism will need increments of levo-thyroxine dose by approximately 25–50% owing to the estrogen-induced rise in TBG plasma concentration. Pregnant women with adequately controlled hypothyroidism are expected not to have an increased risk of pregnancy complications when compared with women without thyroid disease. As far as we know, no randomized controlled trial of T4 substitutive therapy for overt hypothyroidism in pregnant women has been conducted for ethical reasons.

Subclinical hypothyroidism (SCH)

The frequency of subclinical hypothyroidism, biochemically defined as an elevated TSH but a normal free T4, which tends to be asymptomatic, is more prevalent, with a prevalence of 3.5–18%, depending on the TSH values used [60, 61]. The most frequent causes of subclinical hypothyroidism are chronic lymphocytic thyroiditis, and inadequate levo-thyroxine supplementation, poor adherence, drug interactions, or inadequate monitoring of treatment.

Although in the last two decades evidences have accumulated on the possible negative consequences of maternal subclinical hypothyroidism on child development, there is no consensus about the definition of this clinical entity, as well as how and when to treat subclinical hypothyroidism during pregnancy. References range for serum TSH has always been derived from the sera of non-pregnant healthy individuals. Association of American Clinical Endocrinologists (AACE), American Thyroid Association (ATA), Endocrine Society Guidelines (ESG), fixed TSH upper limits of 2.5 mU/l (first and second trimester) and 3.0 mU/l for the third trimester [62–64]. The use of this new threshold, probably resulting in overdiagnosis, or subclinical hypothyroidism, showed that between 8 and 28% of pregnant patients have a TSH concentration above these fixed cutoffs [65–67].

Lowering TSH to <2.5 mU/l has been recommended not only to pregnant women, but also for women planning to become pregnant [52]. Although the adoption of population-based reference ranges would best define gestational thyroid diseases, when these reference ranges are unavailable, recent ATA guidelines advocate the use of a fixed upper limit of the non-pregnancy upper limit minus 0.5 mU/l [59]. Subclinical hypothyroidism during pregnancy has been associated with significant increased risk of placental abruption, early pregnancy loss, neonatal death and pre-eclampsia [68, 69]. Neurodevelopmental deficit in offspring has been described in some studies, but not in others [33, 35, 70]. Data on the effects of treatment for subclinical hypothyroidism are scarce and not univocal. The ATA recommended the treatment of women with subclinical hypothyroidism who have elevated titres of thyroperoxidase antibodies (TPOAb), whereas ETA and the Endocrine Society recommended T4 treatment in all pregnant women with subclinical hypothyroidism, regardless of TPOAb titres [52, 62, 64]. Additional studies showed that T4 replacement in women who were TPOAb-positive decreased the risk of miscarriage or premature delivery [8, 71].

The reported data demonstrated that the benefit of T4 therapy in reducing the risk of preterm delivery was mainly present in patients with TSH levels > 4.0 mU/l [72], since lack of association with altered pregnancy outcomes was demonstrated with variation in thyroid parameters within the normal (non-pregnant) range during the first trimester of pregnancy [73]. Thus, despite the well-defined biochemical guidelines on treatment of overt hypothyroid pregnant women, there is no general consensus on whether to treat SCH women with positive or negative thyroid antibodies.

The TSH threshold for the definition of SCH is also controversial. Recently a higher cutoff value of > 4 U/l has been proposed by ATA. According to the ATA suggestion, T4 replacement could decrease adverse pregnancy outcomes using the newly recommended cutoff, while no beneficial effect was observed in women with TSH cut-point of 2.5–4 U/l [72].

In conclusion, the still accepted general consensus is to treat pregnant women with subclinical hypothyroidism with T4 to achieve a TSH level within the trimester-specific range [74, 75] although the biochemical definition of this clinical condition in pregnancy is still debated.

Thyroid autoimmunity

TPOAb, together with anti-thyroglobulin antibodies (TGAb), are markers of thyroid autoimmunity and often co-exist with other autoimmune disorders [76–78]. Despite a genetic and environmental predisposition being documented [79–84], its etiology is largely unknown. Autoimmune thyroid disease can cause hypothyroidism [85] and other diseases such as thyroid cancer, although the latter is still debatable [86]. Further, it has been considered as important risk factors for thyroid dysfunction during pregnancy, as pregnant women who are antibody-positive have a higher risk of thyroid dysfunction than women who are TPOAb-negative [65, 87, 88]. A beneficial effect of T4 treatment on the risk of premature delivery or miscarriage has been reported in pregnant women [8], particularly in women with TSH levels > 4U/l [74]. The mechanisms through which antithyroid antibodies might increase the risk of adverse pregnant outcomes are not clear. Since TPOAb is a biochemical marker of chronic lymphocytic thyroiditis, pregnant women who are antibody-positive may have a higher risk of thyroid dysfunction and adverse pregnancy outcomes. In keeping with this hypothesis, pregnant women who are TPOAb-negative have a lower risk of adverse pregnancy outcomes than pregnant women who are TPOAb-positive with TSH levels > 4U/l [89–91].

A beneficial effect of T4 replacement therapy on pregnancy outcome in TPOAb-positive women with TSH > 4U/l, or > 2.5U/l has been recently confirmed [72, 92]. A recent meta-analysis demonstrated that subclinical hypothyroidism is a risk factor for miscarriage in women before 20 weeks of pregnancy [7]. The authors recommend early treatments to avoid adverse pregnancy outcomes, although a limitation of the study was the different subclinical hypothyroidism diagnostic criteria of the included study in that review. A dose-dependent relationship between TPOAb and thyroid function on premature delivery risk was recently reported [93].

Isolated maternal hypothyroxinemia

Isolated maternal hypothyroxinemia (IH) refers to a lower serum-free T4 level that is less than 10% or < 5th percentile of the reference in the presence of normal TSH values (< 2.5 mU/l), and negative TPOAb [94]. Initially, hypothyroxinemia was considered a condition of mild iodine deficiency, but hypothyroxinemia also occurs in iodine-sufficient area

and does not tend to increase following iodine supplementation [95, 96]. Thus, not only iodine deficiency but other pathophysiological mechanisms are likely involved in the development of hypothyroxinemia. Potential risk factors include modification for the TBG affinity for T4, increased placental D3 activity, and placental angiogenic factors that have been associated with maternal thyroid function and hCG-mediated free T4 stimulation [97]. Moreover, the coexistence of thyroid autoimmunity has been reported to impair the thyroidal response to hCG [98], whereas the thyroid response to hCG in women with hypothyroxinemia without thyroid autoimmunity was similar to that in euthyroid women [98], suggesting that the condition of hypothyroxinemia was not due to a shortage of thyroid hormone availability.

Overweight might also represent an additional risk factor for hypothyroxinemia in pregnancy [99]. Women who are overweight have a three-to-sixfold higher risk of hypothyroxinemia [100]. Also, additional studies showed that free T4 is negatively correlated with body weight during pregnancy [101, 102]. How overweight may be linked with hypothyroxinemia during a pregnancy is not clear. One hypothesis is that obesity stimulates peripheral deiodinase activity resulting in an increased conversion of free T4-free T3 as an adaptation process to increase energy expenditure. While adverse pregnancy outcomes have been clearly demonstrated in pregnant women with hypothyroidism, data on the consequence of IH on the maternal-fetal unit are not clear and inconsistent [103, 104]. An increased risk of breech presentation at birth has been reported by some authors [99, 105] but not in other reports [106, 107].

Hypothroxinemia may be associated with an increased risk of maternal body mass index (BMI), a susceptibility to develop gestational diabetes and macrosomia although the latter may be related to the higher BMI and gestational diabetes [99]. No benefit in preventing delayed neuropsychological development was reported by treating pregnant women with IH [99]. ATA guidelines did not recommend T4 treatment of gestational hypothyroxinemia, while Endocrine Society guidelines leave it to the discretion of the physician [52, 64]. Nevertheless, T4 therapy in isolated hypothyroxinemia detected in the first trimester (but not in the second and third trimester) was considered by European Thyroid Association [108]. The prevalence of hypothyroxinemia during the first trimester of pregnancy has been reported to be 2–8.7%, although wide differences exist among recent studies. The biochemical diagnostic criteria used are likely the main cause of these discrepancies. Hypothyroxinemia has been considered as either 10th, 5th, or 2.5th lowest percentile of free T4 with negative or positive thyroid autoimmunity. Another confound variable is the iodine status of different populations that has been studied, together with the lack of recommended cutoff values for diagnosis due to important differences between the available assay for free T4. Reference ranges provided by the manufacturers have been established using sera of non-pregnant women. In pregnant women, the results obtained with automated, non-separation assays of free T4 poorly correlate with those obtained by reference method, in which free T4 has been isolated by ultrafiltration or equilibrium dialysis before analysis.

Therefore, additional studies are required to standardize these variables, since the available data do not suggest that hypothyroxinemia may be a laboratory phenomenon due to limited accuracy of free T4 assays in pregnancy [109].

Hyperthyroidism

Maternal hyperthyroidism is defined as suppressed TSH serum level in the presence of high levels of free T4 and/ or free T3. Overt hyperthyroidism during pregnancy is relatively uncommon, occurring in 0.1–0.5% of all pregnancy [24]. The differential diagnosis of thyrotoxicosis in pregnancy is similar to that of non-pregnant women: autoimmune thyroid disorders (Graves' disease, Hashitoxicosis), toxic adenoma or multinodular goiter, transient thyrotoxicosis (subacute thyroiditis, silent thyroiditis), and, rarely, a pituitary secreting TSH.

The most common cause of hyperthyroidism in pregnancy is autoimmune Graves' disease, with circulating TSH receptor antibodies (TRAbs) stimulating the TSH receptor of the thyroid gland. The disease usually exacerbates within the first trimester and tends to improve thereafter [110]. The immune-tolerant state of pregnancy is associated over time with a decrease in TRAb titers and in severity as gestation progresses, but it tends to recur following delivery [23, 24, 111]. Features suggestive of Graves' disease include the presence of ofthalmopathy, TRAb positivity, a family history of autoimmune thyroid disease as well as a pre-existing Graves' disease. The disease often presents with clear symptoms such as palpitations, severe tachycardia, anxiety, tremor, and is associated with clear biochemical abnormality such as suppressed TSH levels with high free T4 or free T3, or both, concentrations. The consequences of untreated or inadequately treated hyperthyroidism can be observed in both mother and fetus [112]. Adverse fetal and maternal outcomes associated with untreated maternal hyperthyroidism include preterm delivery, IUGR, congenital malformations, fetal death and fetal thyrotoxicosis [113]. During pregnancy, there is a transfer of thyroid-stimulating immunoglobulins from the mother to the fetus inducing the activation of the TSH receptor that promotes thyroid hormones secretion and a thyrotoxicosis in utero that remains postnatally [114–117]. Hyperthyroidism in the neonate is rare, usually transient, and remits with clearance of maternal TRAbs in the first 3 months of life [118]. Cardiac failure and thyroid

storm can also occur in pregnant women with uncontrolled hyperthyroidism.

Classical treatment of hyperthyroidism includes the use of antithyroid drugs, surgery or thyroid ablation with I^{131}, the latter being absolutely contraindicated in pregnant patients. When radioiodine therapy has been applied to non-pregnant women, it is advisable to avoid conception for at least 6 months, although this is an empiric recommendation.

The use of antithyroid drugs, namely methimazole, carbimazole, which is a drug to methimazole, and propylthiouracil, has been the standard of care for decades. These compounds block thyroid hormone synthesis, cross the placenta to a varying degree [119], and can have, although rare, adverse effects on the fetus and the fetal thyroid gland, particularly when used during early pregnancy The use of methimazole or carbimazole may be associated with agranulocytosis and a risk of birth defects such as aplasia cutis, facial dysmorphism, omphalocele and choanal atresia [120, 121]. Methimazole exposure in early pregnancy was associated with birth defects in 4.1% of newborns ($p = 0.002$ vs control) [122]. The use of propylthiouracil during pregnancy is predominantly associated with maternal liver injury as well as with an increased risk of cysts, hydronephrosis and preauricular sinuses [120, 121]. The available evidences indicate that the use of propylthiouracil during early pregnancy is likely associated with a slightly lower risk of adverse reactions or outcomes compared with methimazole.

Because available evidence suggests that methimazole may be associated with congenital anomalies, propylthiouracil should be used as a first-line drug, if available, especially during first-trimester organogenesis [123]. Methimazole may be prescribed if propylthiouracil is not available, or if a patient cannot tolerate or has an adverse response to propylthiouracil. For overt hyperthyroidism due to Graves' disease or thyroid nodules, antithyroid drug therapy should be either initiated (for those with new diagnoses) or adjusted (for those with a prior history) to maintain the maternal thyroid hormone levels for free T4 in the upper non-pregnant reference range, as this minimizes the risk of hypothyroidism to the fetus [123]. A surgical approach should be considered in pregnant women with overt hyperthyroidism who have severe adverse reactions to antithyroid drug or when high doses of these compounds are required to achieve an optimal control of the disease.

Thyroid storm is a rare medical emergency, characterized by high levels of thyroid hormones leading to extreme hypermetabolic state. Cardiac arrhythmias, stupor, unexplained fever, altered mental status, confusion, together with a high risk of maternal heart failure are usual clinical pictures. The pharmacological treatment is similar to that of non-pregnant women and requires a multiple pharmacological approach, including high doses of PTU, iodide and corticosteroid therapy, as well as general supportive care. Beta adrenergic blockers are also used to block sympatho-adrenergic hyperactivity. Propranolol has been widely employed: the drug passes the placental barrier with low risk of adverse fetal outcomes. Propranolol has also been demonstrated to reduce circulating T3 levels through a reduction of T4 deiodination [124].

Subclinical hyperthyroidism

Subclinical hyperthyroidism, biochemically defined as a reduced TSH but a normal free T4, usually represents a subclinical form of Graves's disease or uninodular or multinodular goiter. These clinical conditions probably persist throughout the pregnancy and tend to be asymptomatic. The prevalence is about 1.7% and is usually not associated with adverse pregnancy or neonatal outcomes [125]. No pharmacological treatment is usually needed, although the theoretical benefit of lowering thyroid hormones with antithyroid compounds has not been demonstrated.

Gestational transient thyrotoxicosis

Gestational transient thyrotoxicosis is a self-limited non-autoimmune form of hyperthyroidism with negative TRAbs. It is related to the physiological elevation of hCG. The homology between the β subunit of the hCG and TSH molecules cross-reacts with the TSH receptor and induces thyroid hormone secretion. This condition is usually limited to the first half of pregnancy, and is associated with a high free T4 and a TSH that is in the low-to-normal range for pregnancy or is frequently undetectable. As many as 2.4% of women may be affected by this entity during pregnancy [23]. It is suggested that hCG may have a causative role in hyperemesis gravidarum, characterized by excessive nausea and vomiting, which causes dehydration, ketonuria, and a 5% weight loss. The temporal relationship between the level of hCG peak and the severity of vomiting supports this hypothesis. Thus, hyperemesis gravidarum may be considered a mild form of gestational hyperthyroidism, as TSH was found suppressed to below 0.2 mU/l in 60% of women with hyperemesis compared with only 9% of pregnant women without symptoms [126]. However, the exact mechanism for how elevated level of hCG causes hyperemesis is unclear. The vast majority of these patients do not require antithyroid drug therapy, but the administration of low doses of β-blocker may be useful in very symptomatic patients.

Conclusions and take home messages

- Early diagnosis and management of thyroid diseases in pregnancy are essential to avoid severe maternal and fetal clinical complications.
- Low hormone levels during pregnancy can have detrimental effects on the development of the fetus, particularly on the central nervous system.
- Adequate iodine intake is needed for thyroid hormone synthesis and normal neurodevelopment of the fetus.
- Studies of maternal iodine supplementation in iodine-deficient areas have demonstrated reductions in endemic cretinism, rates of fetal death, and improvement of infants' cognitive function.
- Levo-thyroxine requirements in hypothyroid pregnant women increase early in gestation, and T4 doses should target a TSH of 2.5 U/l or less in the first trimester and less than 3.0 U/l in the second and third trimester.
- Subclinical hypothyroidism is often treated with T4, although it has not been proven beyond doubt that it improves fetal outcomes.
- Gestational transient hyperthyroidism as well as subclinical hyperthyroidism do not usually require treatment.
- Overt hyperthyroidism in pregnancy is much less common than hypothyroidism. Antithyroid drugs, particularly propylthiouracil, are recommended in the first trimester of pregnancy.

Author contributions APD: data collection, manuscript writing. GC: data collection, manuscript editing. PLC: manuscript editing. SD: manuscript editing. GD: data collection, manuscript editing.

Funding No funding was received for the preparation of this review.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Delitala AP, Pilia MG, Ferreli L, Loi F, Curreli N, Balaci L, Schlessinger D, Cucca F (2014) Prevalence of unknown thyroid disorders in a Sardinian cohort. Eur J Endocrinol 171:143–149. https://doi.org/10.1530/EJE-14-0182
2. Delitala AP (2017) Subclinical hyperthyroidism and the cardiovascular disease. Horm Metab Res 49:723–731. https://doi.org/10.1055/s-0043-117893
3. Delitala AP, Fanciulli G, Maioli M, Delitala G (2017) Subclinical hypothyroidism, lipid metabolism and cardiovascular disease. Eur J Intern Med 38:17–24. https://doi.org/10.1016/j.ejim.2016.12.015
4. Delitala AP, Fanciulli G, Pes GM, Maioli M, Delitala G (2017) Thyroid hormones, metabolic syndrome and its components. Endocr Metab Immune Disord Drug Targets 17:56–62. https://doi.org/10.2174/1871530317666170320105221
5. Delitala AP, Terracciano A, Fiorillo E, Orru V, Schlessinger D, Cucca F (2016) Depressive symptoms, thyroid hormone and autoimmunity in a population-based cohort from Sardinia. J Affect Disord 191:82–87. https://doi.org/10.1016/j.jad.2015.11.019
6. Kim JS, Zhang Y, Chang Y, Ryu S, Guallar E, Shin YC, Shin H, Lim SW, Cho J (2018) Subclinical hypothyroidism and incident depression in young and middle age adults. J Clin Endocrinol Metab. https://doi.org/10.1210/jc.2017-01247
7. Zhang Y, Wang H, Pan X, Teng W, Shan Z (2017) Patients with subclinical hypothyroidism before 20 weeks of pregnancy have a higher risk of miscarriage: a systematic review and meta-analysis. PLoS ONE 12:e0175708. https://doi.org/10.1371/journal.pone.0175708
8. van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JA, Goddijn M, Bisschop PH (2011) Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Hum Reprod Update 17:605–619. https://doi.org/10.1093/humupd/dmr024
9. Giacobbe AM, Grasso R, Triolo O, Tonni G, Granese R (2015) Thyroid diseases in pregnancy: a current and controversial topic on diagnosis and treatment over the past 20 years. Arch Gynecol Obstet 292:995–1002. https://doi.org/10.1007/s00404-015-3741-y
10. Bianco AC, Larsen PR (2005) Cellular and structural biology of the deiodinases. Thyroid 15:777–786. https://doi.org/10.1089/thy.2005.15.777
11. Calvo RM, Jauniaux E, Gulbis B, Asuncion M, Gervy C, Contempre B, Morreale de Escobar G (2002) Fetal tissues are exposed to biologically relevant free thyroxine concentrations during early phases of development. J Clin Endocrinol Metab 87:1768–1777. https://doi.org/10.1210/jcem.87.4.8434
12. Burman KD, Read J, Dimond RC, Strum D, Wright FD, Patow W, Earll JM, Wartofsky L (1976) Measurement of 3,3',5'-Triiodothyroinine (reverse T3), 3,3'-L-diiodothyronine, T3 and T4 in human amniotic fluid and in cord and maternal serum. J Clin Endocrinol Metab 43:1351–1359. https://doi.org/10.1210/jcem-43-6-1351
13. Williams GR (2008) Neurodevelopmental and neurophysiological actions of thyroid hormone. J Neuroendocrinol 20:784–794. https://doi.org/10.1111/j.1365-2826.2008.01733.x
14. Zhang J, Lazar MA (2000) The mechanism of action of thyroid hormones. Annu Rev Physiol 62:439–466. https://doi.org/10.1146/annurev.physiol.62.1.439
15. Klein I, Ojamaa K (2001) Thyroid hormone and the cardiovascular system. N Engl J Med 344:501–509. https://doi.org/10.1056/NEJM200102153440707
16. Delitala AP, Orru M, Filigheddu F, Pilia MG, Delitala G, Ganau A, Saba PS, Decandia F, Scuteri A, Marongiu M, Lakatta EG, Strait J, Cucca F (2015) Serum free thyroxine levels are positively associated with arterial stiffness in the SardiNIA study. Clin Endocrinol (Oxf) 82:592–597. https://doi.org/10.1111/cen.12532
17. Amouzegar A, Heidari M, Gharibzadeh S, Mehran L, Tohidi M, Azizi F (2016) The association between blood pressure and normal range thyroid function tests in a population based Tehran thyroid study. Horm Metab Res 48:151–156. https://doi.org/10.1055/s-0035-1564131
18. Delitala AP, Steri M, Pilia MG, Dei M, Lai S, Delitala G, Schlessinger D, Cucca F (2016) Menopause modulates the association between thyrotropin levels and lipid parameters: the SardiNIA study. Maturitas 92:30–34. https://doi.org/10.1016/j.maturitas.2016.07.003

19. Delitala AP, Delitala G, Sioni P, Fanciulli G (2017) Thyroid hormone analogs for the treatment of dyslipidemia: past, present, and future. Curr Med Res Opin 33:1985–1993. https://doi.org/10.1080/03007995.2017.1330259
20. Volzke H, Robinson DM, Schminke U, Ludemann J, Rettig R, Felix SB, Kessler C, John U, Meng W (2004) Thyroid function and carotid wall thickness. J Clin Endocrinol Metab 89:2145–2149. https://doi.org/10.1210/jc.2003-031028
21. Delitala AP, Filigheddu F, Orru M, AlGhatrif M, Steri M, Pilia MG, Scuteri A, Lobina M, Piras MG, Delitala G, Lakatta EG, Schlessinger D, Cucca F (2015) No evidence of association between subclinical thyroid disorders and common carotid intima medial thickness or atherosclerotic plaque. Nutr Metab Cardiovasc Dis 25:1104–1110. https://doi.org/10.1016/j.numecd.2015.09.001
22. Carreon-Rodriguez A, Perez-Martinez L (2012) Clinical implications of thyroid hormones effects on nervous system development. Pediatr Endocrinol Rev 9:644–649
23. Glinoer D (1997) The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev 18:404–433. https://doi.org/10.1210/edrv.18.3.0300
24. Krassas GE, Poppe K, Glinoer D (2010) Thyroid function and human reproductive health. Endocr Rev 31:702–755. https://doi.org/10.1210/er.2009-0041
25. Auso E, Lavado-Autric R, Cuevas E, Del Rey FE, Morreale De Escobar G, Berbel P (2004) A moderate and transient deficiency of maternal thyroid function at the beginning of fetal neocorticogenesis alters neuronal migration. Endocrinology 145:4037–4047. https://doi.org/10.1210/en.2004-0274
26. Korevaar TI, Muetzel R, Medici M, Chaker L, Jaddoe VW, de Rijke YB, Steegers EA, Visser TJ, White T, Tiemeier H, Peeters RP (2016) Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. Lancet Diabetes Endocrinol 4:35–43. https://doi.org/10.1016/S2213-8587(15)00327-7
27. Fisher DA, Klein AH (1981) Thyroid development and disorders of thyroid function in the newborn. N Engl J Med 304:702–712. https://doi.org/10.1056/NEJM198103193041205
28. Chen ZP, Hetzel BS (2010) Cretinism revisited. Best Pract Res Clin Endocrinol Metab 24:39–50. https://doi.org/10.1016/j.beem.2009.08.014
29. Ahmed OM, Abd El-Tawab SM, Ahmed RG (2010) Effects of experimentally induced maternal hypothyroidism and hyperthyroidism on the development of rat offspring: I. The development of the thyroid hormones-neurotransmitters and adenosinergic system interactions. Int J Dev Neurosci 28:437–454. https://doi.org/10.1016/j.ijdevneu.2010.06.007
30. Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL (1999) Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf) 50:149–155
31. Smit BJ, Kok JH, Vulsma T, Briet JM, Boer K, Wiersinga WM (2000) Neurologic development of the newborn and young child in relation to maternal thyroid function. Acta Paediatr 89:291–295
32. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ (2003) Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf) 59:282–288
33. Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, Hooijkaas H, de Muinck Keizer-Schrama SM, Hofman A, Jaddoe VV, Visser W, Steegers EA, Verhulst FC, de Rijke YB, Tiemeier H (2010) Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. J Clin Endocrinol Metab 95:4227–4234. https://doi.org/10.1210/jc.2010-0415
34. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, Teng X, Guo R, Wang H, Li J, Chen Y, Wang W, Chawinga M, Zhang L, Yang L, Zhao Y, Hua T (2010) Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25–30 months. Clin Endocrinol (Oxf) 72:825–829. https://doi.org/10.1111/j.1365-2265.2009.03743.x
35. Ghassabian A, Bongers-Schokking JJ, Henrichs J, Jaddoe VW, Visser TJ, Visser W, de Muinck Keizer-Schrama SM, Hooijkaas H, Steegers EA, Hofman A, Verhulst FC, van der Ende J, de Rijke YB, Tiemeier H (2011) Maternal thyroid function during pregnancy and behavioral problems in the offspring: the generation R study. Pediatr Res 69:454–459. https://doi.org/10.1203/PDR.0b013e3182125b0c
36. Ghassabian A, El Marroun H, Peeters RP, Jaddoe VW, Hofman A, Verhulst FC, Tiemeier H, White T (2014) Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal IQ and brain morphology in school-age children. J Clin Endocrinol Metab 99:2383–2390. https://doi.org/10.1210/jc.2013-4281
37. Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, Castagna MG, Mattina F, Violi MA, Crisa A, Artemisia A, Trimarchi F (2004) Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. J Clin Endocrinol Metab 89:6054–6060. https://doi.org/10.1210/jc.2004-0571
38. Oostenbroek MHW, Kersten RHJ, Tros B, Kunst AE, Vrijkotte TGM, Finken MJJ (2017) Maternal hypothyroxinaemia in early pregnancy and problem behavior in 5-year-old offspring. Psychoneuroendocrinology 81:29–35. https://doi.org/10.1016/j.psyneuen.2017.03.021
39. Oken E, Braverman LE, Platek D, Mitchell ML, Lee SL, Pearce EN (2009) Neonatal thyroxine, maternal thyroid function, and child cognition. J Clin Endocrinol Metab 94:497–503. https://doi.org/10.1210/jc.2008-0936
40. Craig WY, Allan WC, Kloza EM, Pulkkinen AJ, Waisbren S, Spratt DI, Palomaki GE, Neveux LM, Haddow JE (2012) Mid-gestational maternal free thyroxine concentration and offspring neurocognitive development at age two years. J Clin Endocrinol Metab 97:E22–E28. https://doi.org/10.1210/jc.2011-1772
41. Opazo MC, Haensgen H, Bohmwald K, Venegas LF, Boudin H, Elorza AA, Simon F, Fardella C, Bueno SM, Kalergis AM, Riedel CA (2017) Imprinting of maternal thyroid hormones in the offspring. Int Rev Immunol 36:240–255. https://doi.org/10.1080/08830185.2016.1277216
42. Willoughby KA, McAndrews MP, Rovet JF (2014) Effects of maternal hypothyroidism on offspring hippocampus and memory. Thyroid 24:576–584. https://doi.org/10.1089/thy.2013.0215
43. Samadi A, Skocic J, Rovet JF (2015) Children born to women treated for hypothyroidism during pregnancy show abnormal corpus callosum development. Thyroid 25:494–502. https://doi.org/10.1089/thy.2014.0548
44. Lischinsky JE, Skocic J, Clairman H, Rovet J (2016) Preliminary findings show maternal hypothyroidism may contribute to abnormal cortical morphology in offspring. Front Endocrinol (Lausanne) 7:16. https://doi.org/10.3389/fendo.2016.00016
45. Zimmermann MB, Jooste PL, Pandav CS (2008) Iodine-deficiency disorders. Lancet 372:1251–1262. https://doi.org/10.1016/S0140-6736(08)61005-3
46. Glinoer D (2007) The importance of iodine nutrition during pregnancy. Public Health Nutr 10:1542–1546. https://doi.org/10.1017/S1368980007360886

47. Dafnis E, Sabatini S (1992) The effect of pregnancy on renal function: physiology and pathophysiology. Am J Med Sci 303:184–205
48. Leung AM, Pearce EN, Braverman LE (2011) Iodine nutrition in pregnancy and lactation. Endocrinol Metab Clin North Am 40:765–777. https://doi.org/10.1016/j.ecl.2011.08.001
49. Boyages SC (1993) Clinical review 49: Iodine deficiency disorders. J Clin Endocrinol Metab 77:587–591. https://doi.org/10.1210/jcem.77.3.8370679
50. de Escobar GM, Obregon MJ, del Rey FE (2007) Iodine deficiency and brain development in the first half of pregnancy. Public Health Nutr 10:1554–1570. https://doi.org/10.1017/S1368980007360928
51. Li M, Eastman CJ (2010) Neonatal TSH screening: is it a sensitive and reliable tool for monitoring iodine status in populations? Best Pract Res Clin Endocrinol Metab 24:63–75. https://doi.org/10.1016/j.beem.2009.08.007
52. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W, American Thyroid Association Taskforce on Thyroid Disease During P, Postpartum (2011) Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 21:1081–1125. https://doi.org/10.1089/thy.2011.0087
53. Vaidya B, Anthony S, Bilous M, Shields B, Drury J, Hutchison S, Bilous R (2007) Detection of thyroid dysfunction in early pregnancy: Universal screening or targeted high-risk case finding? J Clin Endocrinol Metab 92:203–207. https://doi.org/10.1210/jc.2006-1748
54. Medici M, Korevaar TI, Visser WE, Visser TJ, Peeters RP (2015) Thyroid function in pregnancy: what is normal? Clin Chem 61:704–713. https://doi.org/10.1373/clinchem.2014.236646
55. Pop V, Broeren M, Wiersinga W (2014) The attitude toward hypothyroidism during early gestation: time for a change of mind? Thyroid 24:1541–1546. https://doi.org/10.1089/thy.2014.0007
56. Saki F, Dabbaghmanesh MH, Ghaemi SZ, Forouhari S, Ranjbar Omrani G, Bakhshayeshkaram M (2014) Thyroid function in pregnancy and its influences on maternal and fetal outcomes. Int J Endocrinol Metab 12:e19378. https://doi.org/10.5812/ijem.19378
57. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ (1999) Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341:549–555. https://doi.org/10.1056/NEJM199908193410801
58. Tingi E, Syed AA, Kyriacou A, Mastorakos G, Kyriacou A (2016) Benign thyroid disease in pregnancy: a state of the art review. J Clin Transl Endocrinol 6:37–49. https://doi.org/10.1016/j.jcte.2016.11.001
59. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S (2017) 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 27:315–389. https://doi.org/10.1089/thy.2016.0457
60. Blatt AJ, Nakamoto JM, Kaufman HW (2012) National status of testing for hypothyroidism during pregnancy and postpartum. J Clin Endocrinol Metab 97:777–784. https://doi.org/10.1210/jc.2011-2038
61. Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RJ, Pulkkinen A, Mitchell ML (1991) Prevalence of thyroid deficiency in pregnant women. Clin Endocrinol (Oxf) 35:41–46
62. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B (2014) 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur Thyroid J 3:76–94. https://doi.org/10.1159/000362597
63. Stagnaro-Green A (2011) Overt hyperthyroidism and hypothyroidism during pregnancy. Clin Obstet Gynecol 54:478–487. https://doi.org/10.1097/GRF.0b013e3182272f32
64. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, Eastman CJ, Lazarus JH, Luton D, Mandel SJ, Mestman J, Rovet J, Sullivan S (2012) Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 97:2543–2565. https://doi.org/10.1210/jc.2011-2803
65. Medici M, Timmermans S, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VW, Hofman A, Hooijkaas H, de Rijke YB, Tiemeier H, Bongers-Schokking JJ, Visser TJ, Peeters RP, Steegers EA (2013) Maternal thyroid hormone parameters during early pregnancy and birth weight: the Generation R Study. J Clin Endocrinol Metab 98:59–66. https://doi.org/10.1210/jc.2012-2420
66. Li C, Shan Z, Mao J, Wang W, Xie X, Zhou W, Li C, Xu B, Bi L, Meng T, Du J, Zhang S, Gao Z, Zhang X, Yang L, Fan C, Teng W (2014) 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 99:73–79. https://doi.org/10.1210/jc.2013-1674
67. Korevaar TIM, Medici M, Visser TJ, Peeters RP (2017) Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nat Rev Endocrinol 13:610–622. https://doi.org/10.1038/nrendo.2017.93
68. Liu H, Shan Z, Li C, Mao J, Xie X, Wang W, Fan C, Wang H, Zhang H, Han C, Wang X, Liu X, Fan Y, Bao S, Teng W (2014) Maternal subclinical hypothyroidism, thyroid autoimmunity, and the risk of miscarriage: a prospective cohort study. Thyroid 24:1642–1649. https://doi.org/10.1089/thy.2014.0029
69. Maraka S, Singh Ospina NM, O'Keeffe DT, Rodriguez-Gutierrez R, Espinosa De Ycaza AE, Wi CI, Juhn YJ, Coddington CC 3rd, Montori VM, Stan MN (2016) Effects of levothyroxine therapy on pregnancy outcomes in women with subclinical hypothyroidism. Thyroid 26:980–986. https://doi.org/10.1089/thy.2016.0014
70. Behrooz HG, Tohidi M, Mehrabi Y, Behrooz EG, Tehranidoost M, Azizi F (2011) Subclinical hypothyroidism in pregnancy: intellectual development of offspring. Thyroid 21:1143–1147. https://doi.org/10.1089/thy.2011.0053
71. Korevaar TI, Chaker L, Jaddoe VW, Visser TJ, Medici M, Peeters RP (2016) Maternal and birth characteristics are determinants of offspring thyroid function. J Clin Endocrinol Metab 101:206–213. https://doi.org/10.1210/jc.2015-3559
72. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Minooee S, Rahmati M, Azizi F (2017) Effects of Levothyroxine on pregnant women with subclinical hypothyroidism, negative for thyroid peroxidase antibodies. J Clin Endocrinol Metab. https://doi.org/10.1210/jc.2017-01850
73. Veltri F, Kleynen P, Grabczan L, Salajan A, Rozenberg S, Pepersack T, Poppe K (2018) Pregnancy outcomes are not altered by variation in thyroid function within the normal range in women free of thyroid disease. Eur J Endocrinol 178:191–199. https://doi.org/10.1530/EJE-17-0628
74. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Alavi Majd H, Azizi F (2017) Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. Eur J Endocrinol 176:253–265. https://doi.org/10.1530/EJE-16-0548
75. Lazarus JH (2014) Management of hyperthyroidism in pregnancy. Endocrine 45:190–194. https://doi.org/10.1007/s12020-013-0086-9

76. Ch'ng CL, Jones MK, Kingham JG (2007) Celiac disease and autoimmune thyroid disease. Clin Med Res 5:184–192. https://doi.org/10.3121/cmr.2007.738
77. Delitala AP, Fanciulli G, Zoledziewska M, Pitzalis M, Pusceddu P, Frongia P, Puddu L, Errigo A, Maioli M, Delitala G, Pes GM (2015) Allelic variant in CTLA4 is associated with thyroid failure and faster beta-cell exhaustion in latent autoimmune diabetes in adults. J Diabetes 7:68–73
78. Van den Driessche A, Eenkhoorn V, Van Gaal L, De Block C (2009) Type 1 diabetes and autoimmune polyglandular syndrome: a clinical review. Neth J Med 67:376–387
79. Tomer Y, Davies TF (2003) Searching for the autoimmune thyroid disease susceptibility genes: from gene mapping to gene function. Endocr Rev 24:694–717. https://doi.org/10.1210/er.2002-0030
80. Medici M, Porcu E, Pistis G, Teumer A, Brown SJ, Jensen RA, Rawal R, Roef GL, Plantinga TS, Vermeulen SH, Lahti J, Simmonds MJ, Husemoen LL, Freathy RM, Shields BM, Pietzner D, Nagy R, Broer L, Chaker L, Korevaar TI, Plia MG, Sala C, Volker U, Richards JB, Sweep FC, Gieger C, Corre T, Kajantie E, Thuesen B, Taes YE, Visser WE, Hattersley AT, Kratzsch J, Hamilton A, Li W, Homuth G, Lobina M, Mariotti S, Soranzo N, Cocca M, Nauck M, Spielhagen C, Ross A, Arnold A, van de Bunt M, Liyanarachchi S, Heier M, Grabe HJ, Masciullo C, Galesloot TE, Lim EM, Reischl E, Leedman PJ, Lai S, Delitala A, Bremner AP, Philips DI, Beilby JP, Mulas A, Vocale M, Abecasis G, Forsen T, James A, Widen E, Hui J, Prokisch H, Rietzschel EE, Palotie A, Feddema P, Fletcher SJ, Schramm K, Rotter JI, Kluttig A, Radke D, Traglia M, Surdulescu GL, He H, Franklyn JA, Tiller D, Vaidya B, de Meyer T, Jorgensen T, Eriksson JG, O'Leary PC, Wichmann E, Hermus AR, Psaty BM, Ittermann T, Hofman A, Bosi E, Schlessinger D, Wallaschofski H, Pirastu N, Aulchenko YS, de la Chapelle A, Netea-Maier RT, Gough SC, Meyer Zu Schwabedissen H, Frayling TM, Kaufman JM, Linneberg A, Raikkonen K, Smit JW, Kiemeney LA, Rivadeneira F, Uitterlinden AG, Walsh JP, Meisinger C, den Heijer M, Visser TJ, Spector TD, Wilson SG, Volzke H, Cappola A, Toniolo D, Sanna S, Naitza S, Peeters RP (2014) Identification of novel genetic Loci associated with thyroid peroxidase antibodies and clinical thyroid disease. PLoS Genet 10:e1004123. https://doi.org/10.1371/journal.pgen.1004123
81. Delitala AP, Steri M, Fiorillo E, Marongiu M, Lakatta EG, Schlessinger D, Cucca F (2018) Adipocytokine correlations with thyroid function and autoimmunity in euthyroid sardinians. Cytokine 111:189–193. https://doi.org/10.1016/j.cyto.2018.08.027
82. Delitala AP, Sanciu FA, Errigo A, Delitala G, Pes GM (2017) Leptin levels and insulin dependence in latent autoimmune diabetes in adults. J Interferon Cytokine Res 37:550–556. https://doi.org/10.1089/jir.2017.0059
83. Kachuei M, Jafari F, Kachuei A, Keshteli AH (2012) Prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. Arch Gynecol Obstet 285:853–856. https://doi.org/10.1007/s00404-011-2040-5
84. Delitala AP, Capobianco G, Delitala G, Cherchi PL, Dessole S (2017) Polycystic ovary syndrome, adipose tissue and metabolic syndrome. Arch Gynecol Obstet 296:405–419. https://doi.org/10.1007/s00404-017-4429-2
85. Weetman AP, McGregor AM (1994) Autoimmune thyroid disease: further developments in our understanding. Endocr Rev 15:788–830. https://doi.org/10.1210/edrv-15-6-788
86. Fiore E, Rago T, Latrofa F, Provenzale MA, Piaggi P, Delitala A, Scutari M, Basolo F, Di Coscio G, Grasso L, Pinchera A, Vitti P (2011) Hashimoto's thyroiditis is associated with papillary thyroid carcinoma: role of TSH and of treatment with L-thyroxine. Endocr Relat Cancer 18(4):429–37
87. Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A (2011) Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. BMJ 342:d2616. https://doi.org/10.1136/bmj.d2616
88. Kumru P, Erdogdu E, Arisoy R, Demirci O, Ozkoral A, Ardic C, Ertekin AA, Erdogan S, Ozdemir NN (2015) Effect of thyroid dysfunction and autoimmunity on pregnancy outcomes in low risk population. Arch Gynecol Obstet 291:1047–1054. https://doi.org/10.1007/s00404-014-3533-9
89. Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, Visser WE, Visser W, de Muinck Keizer-Schrama SM, Hofman A, Ross HA, Hooijkaas H, Tiemeier H, Bongers-Schokking JJ, Jaddoe VW, Visser TJ, Steegers EA, Medici M, Peeters RP (2013) Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the generation R study. J Clin Endocrinol Metab 98:4382–4390. https://doi.org/10.1210/jc.2013-2855
90. Karakosta P, Alegakis D, Georgiou V, Roumeliotaki T, Fthenou E, Vassilaki M, Boumpas D, Castanas E, Kogevinas M, Chatzi L (2012) Thyroid dysfunction and autoantibodies in early pregnancy are associated with increased risk of gestational diabetes and adverse birth outcomes. J Clin Endocrinol Metab 97:4464–4472. https://doi.org/10.1210/jc.2012-2540
91. Challis BG, Powlson AS, Casey RT, Pearson C, Lam BY, Ma M, Pitfield D, Yeo GSH, Godfrey E, Cheow HK, Chatterjee VK, Carroll NR, Shaw A, Buscombe JR, Simpson HL (2017) Adult-onset hyperinsulinaemic hypoglycaemia in clinical practice: diagnosis, aetiology and management. Endocr Connect 6:540–548. https://doi.org/10.1530/EC-17-0076
92. Blumenthal NJ, Eastman CJ (2017) Beneficial effects on pregnancy outcomes of thyroid hormone replacement for subclinical hypothyroidism. J Thyroid Res 2017:4601365. https://doi.org/10.1155/2017/4601365
93. Korevaar TIM, Pop VJ, Chaker L, Goddijn M, de Rijke YB, Bisschop PH, Broeren MA, Jaddoe VWV, Medici M, Visser TJ, Steegers EAP, Vrijkotte TG, Peeters RP (2018) Dose dependency and a functional cutoff for TPO-antibody positivity during pregnancy. J Clin Endocrinol Metab 103:778–789. https://doi.org/10.1210/jc.2017-01560
94. Negro R, Soldin OP, Obregon MJ, Stagnaro-Green A (2011) Hypothyroxinemia and pregnancy. Endocr Pract 17:422–429. https://doi.org/10.4158/EP10309.RA
95. Zimmermann MB (2007) The adverse effects of mild-to-moderate iodine deficiency during pregnancy and childhood: a review. Thyroid 17:829–835. https://doi.org/10.1089/thy.2007.0108
96. Zimmermann MB, Gizak M, Abbott K, Andersson M, Lazarus JH (2015) Iodine deficiency in pregnant women in Europe. Lancet Diabetes Endocrinol 3:672–674. https://doi.org/10.1016/S2213-8587(15)00263-6
97. Korevaar TI, Steegers EA, de Rijke YB, Visser WE, Jaddoe VW, Visser TJ, Medici M, Peeters RP (2015) Placental angiogenic factors are associated with maternal thyroid function and modify hCG-mediated FT4 stimulation. J Clin Endocrinol Metab 100:E1328–E1334. https://doi.org/10.1210/jc.2015-2553
98. Korevaar TIM, Steegers EAP, Chaker L, Medici M, Jaddoe VWV, Visser TJ, de Rijke YB, Peeters RP (2017) Thyroid function and premature delivery in TPO antibody-negative women: the added value of hCG. J Clin Endocrinol Metab 102:3360–3367. https://doi.org/10.1210/jc.2017-00846
99. Furnica RM, Gruson D, Lazarus JH, Maiter D, Bernard P, Daumerie C (2017) First trimester isolated maternal hypothyroxinaemia: adverse maternal metabolic profile and impact on the obstetrical outcome. Clin Endocrinol (Oxf) 86:576–583. https://doi.org/10.1111/cen.13301

100. Gowachirapant S, Melse-Boonstra A, Winichagoon P, Zimmermann MB (2014) Overweight increases risk of first trimester hypothyroxinaemia in iodine-deficient pregnant women. Matern Child Nutr 10:61–71. https://doi.org/10.1111/mcn.12040
101. Pop VJ, Biondi B, Wijnen HA, Kuppens SM, Lvader H (2013) Maternal thyroid parameters, body mass index and subsequent weight gain during pregnancy in healthy euthyroid women. Clin Endocrinol (Oxf) 79:577–583. https://doi.org/10.1111/cen.12177
102. Haddow JE, Craig WY, Palomaki GE, Neveux LM, Lambert-Messerlian G, Canick JA, Malone FD, D'Alton ME, First, Second Trimester Risk Of Aneuploidy Faster Research C (2013) Impact of adjusting for the reciprocal relationship between maternal weight and free thyroxine during early pregnancy. Thyroid 23:225–230. https://doi.org/10.1089/thy.2012.0440
103. Casey BM, Dashe JS, Spong CY, McIntire DD, Leveno KJ, Cunningham GF (2007) Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. Obstet Gynecol 109:1129–1135. https://doi.org/10.1097/01.AOG.0000262054.03531.24
104. Hamm MP, Cherry NM, Martin JW, Bamforth F, Burstyn I (2009) The impact of isolated maternal hypothyroxinemia on perinatal morbidity. J Obstet Gynaecol Can 31:1015–1021. https://doi.org/10.1016/S1701-2163(16)34345-6
105. Pop VJ, Brouwers EP, Wijnen H, Oei G, Essed GG, Vader HL (2004) Low concentrations of maternal thyroxin during early gestation: a risk factor of breech presentation? BJOG 111:925–930. https://doi.org/10.1111/j.1471-0528.2004.00213.x
106. Kuppens SM, Kooistra L, Wijnen HA, Crawford S, Vader HL, Hasaart TH, Oei SG, Pop VJ (2010) Maternal thyroid function during gestation is related to breech presentation at term. Clin Endocrinol (Oxf) 72:820–824. https://doi.org/10.1111/j.1365-2265.2009.03729.x
107. Salehidobakhshari M, Bamforth F, Burstyn I (2010) Maternal thyroid hormones in early pregnancy and risk of breech presentation. J Obstet Gynaecol Can 32:948–955
108. Lazarus JH (2014) Iodine status in Europe in 2014. Eur Thyroid J 3:3–6. https://doi.org/10.1159/000358873
109. Roti E, Gardini E, Minelli R, Bianconi L, Flisi M (1991) Thyroid function evaluation by different commercially available free thyroid hormone measurement kits in term pregnant women and their newborns. J Endocrinol Investig 14:1–9. https://doi.org/10.1007/BF03350244
110. Nguyen CT, Sasso EB, Barton L, Mestman JH (2018) Graves' hyperthyroidism in pregnancy: a clinical review. Clin Diabetes Endocrinol 4:4. https://doi.org/10.1186/s40842-018-0054-7
111. Patil-Sisodia K, Mestman JH (2010) Graves hyperthyroidism and pregnancy: a clinical update. Endocr Pract 16:118–129. https://doi.org/10.4158/EP09233.RA
112. Kinomoto-Kondo S, Umehara N, Sato S, Ogawa K, Fujiwara T, Arata N, Sago H (2017) The effects of gestational transient thyrotoxicosis on the perinatal outcomes: a case-control study. Arch Gynecol Obstet 295:87–93. https://doi.org/10.1007/s00404-016-4219-2
113. King JR, Lachica R, Lee RH, Montoro M, Mestman J (2016) Diagnosis and management of hyperthyroidism in pregnancy: a review. Obstet Gynecol Surv 71:675–685. https://doi.org/10.1097/OGX.0000000000000367
114. Momotani N, Ito K, Hamada N, Ban Y, Nishikawa Y, Mimura T (1984) Maternal hyperthyroidism and congenital malformation in the offspring. Clin Endocrinol (Oxf) 20:695–700
115. Pillar N, Levy A, Holcberg G, Sheiner E (2010) Pregnancy and perinatal outcome in women with hyperthyroidism. Int J Gynaecol Obstet 108:61–64. https://doi.org/10.1016/j.ijgo.2009.08.006
116. Anselmo J, Cao D, Karrison T, Weiss RE, Refetoff S (2004) Fetal loss associated with excess thyroid hormone exposure. JAMA 292:691–695. https://doi.org/10.1001/jama.292.6.691
117. Krajewski DA, Burman KD (2011) Thyroid disorders in pregnancy. Endocrinol Metab Clin North Am 40:739–763. https://doi.org/10.1016/j.ecl.2011.08.004
118. Papendieck P, Chiesa A, Prieto L, Gruneiro-Papendieck L (2009) Thyroid disorders of neonates born to mothers with Graves' disease. J Pediatr Endocrinol Metab 22:547–553
119. Mortimer RH, Cannell GR, Addison RS, Johnson LP, Roberts MS, Bernus I (1997) Methimazole and propylthiouracil equally cross the perfused human term placental lobule. J Clin Endocrinol Metab 82:3099–3102. https://doi.org/10.1210/jcem.82.9.4210
120. Laurberg P, Andersen SL (2015) Antithyroid Drug Use in Pregnancy and Birth Defects: Why Some Studies Find Clear Associations, and Some Studies Report None. Thyroid 25:1185–1190. https://doi.org/10.1089/thy.2015.0182
121. Takata K, Kubota S, Fukata S, Kudo T, Nishihara E, Ito M, Amino N, Miyauchi A (2009) Methimazole-induced agranulocytosis in patients with Graves' disease is more frequent with an initial dose of 30 mg daily than with 15 mg daily. Thyroid 19:559–563. https://doi.org/10.1089/thy.2008.0364
122. Yoshihara A, Noh J, Yamaguchi T, Ohye H, Sato S, Sekiya K, Kosuga Y, Suzuki M, Matsumoto M, Kunii Y, Watanabe N, Mukasa K, Ito K, Ito K (2012) Treatment of graves' disease with antithyroid drugs in the first trimester of pregnancy and the prevalence of congenital malformation. J Clin Endocrinol Metab 97:2396–2403. https://doi.org/10.1210/jc.2011-2860
123. Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoer D, Mandel SJ, Stagnaro-Green A (2007) Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 92:S1–S47. https://doi.org/10.1210/jc.2007-0141
124. Lotti G, Delitala G, Devilla L, Alagna S, Masala A (1977) Reduction of plasma triiodothyronine (T3) induced by propranolol. Clin Endocrinol (Oxf) 6:405–410
125. Casey BM, Dashe JS, Wells CE, McIntire DD, Leveno KJ, Cunningham FG (2006) Subclinical hyperthyroidism and pregnancy outcomes. Obstet Gynecol 107:337–341. https://doi.org/10.1097/01.AOG.0000197991.64246.9a
126. Goodwin TM, Montoro M, Mestman JH, Pekary AE, Hershman JM (1992) The role of chorionic gonadotropin in transient hyperthyroidism of hyperemesis gravidarum. J Clin Endocrinol Metab 75:1333–1337. https://doi.org/10.1210/jcem.75.5.1430095