Thyroid physiology and common diseases in pregnancy: review of literature

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Summary

Thyroid diseases are common during pregnancy and an adequate treatment is important to prevent adverse maternal and fetal outcomes. Subclinical diseases are very frequent but not easily recognized without specific screening programs. In this article we try to summarize the knowledge on the physiologic change of the thyroid and pathological function during pregnancy; we also try to describe the best way of diagnosis and treatment of thyroid dysfunction.

Key words: thyroid, pregnancy, hypothyroidism, hyperthyroidism, anti-thyroid drugs.

Introduction

Thyroid disorders are common in pregnancy and related to maternal and fetal complications.
Hyperthyroidism occurs in 0.1-0.4% of pregnant women. Whereas about 2-3% of pregnant women are hypothyroid, of whom 0.3-0.5% have overt hypothyroidism and 2-2.5% present subclinical hypothyroidism (1).
At least 5-10% of women are positive for thyroid antibodies and have an increased risk of developing a certain degree of thyroid insufficiency during pregnancy (2).
Thyroid function is influenzed by pregnancy and its dysfunction is associated with maternal and fetal morbidity. Moreover the role of subclinical hypothyroidism in the developement of fetal and maternal complications is not univocal (3). Indeed subclinical hyperthyroidism is not associated with adverse outcomes. Thyroid autoimmunity appears to be associated with an increased risk of miscarriage and preterm delivery (4).
In this article we aimed to review the possible adverse maternal and fetal outcomes of thyroid during pregnancy and the proper management of these conditions to avoid such complications.

Methods and materials

We searched on PubMed using a combination of MeSH and text words to generate two subsets of quotes combined with "AND", one indexing thyroid disease and the other indexing maternal and fetal outcomes.
Language restrictions were applied and the authors have considered only articles in English, Italian or French. We excluded all the articles whose abstract was not available.
The electronic searches were scrutinised and we obtained full manuscripts of all quotes considered relevant to our study.

Physiology of maternal and fetal thyroid in pregnancy

The thyroid undergoes physiological changes during pregnancy, such moderate enlargement of the gland and increasing of vascularization. Beta-Human chorionic gonadotropin (∞-HCG) causes thyroid stimulation since the first trimester, due to structural analogy with thyroid-stimulating hormone (TSH) (5). The thyrotropic activity of ∞-hCG causes also a decrease in serum TSH in the first trimester so that pregnant women have lower serum TSH concentrations than non-pregnant women (6).
The circulating levels of thyroid-binding globulin (TBG) are also increased by estrogen stimulation. On the other hand the increased renal clearance both fetal intake and placenta metabolism induce a relative decline in the availability of iodide (7).
The circulating level of TBG increases, thanks to increased hepatic synthesis and estrogen mediated prolongation of TBG half-life from 15 minutes to 3 days, a few weeks after conception and reaches a plateau during mid-gestation (8).
Total concentrations of thyroxine (T4) and of triiodothyronine (T3) increase in early pregnancy and achieve a plateau early in the second trimester, reaching a concentrations value of 30-100% greater than prepregnancy, primarily following the rise in TBG (9).
Some authors have reported a decrease of free T4 and T3 concentrations, whereas others have reported no change or even an increase; therefore changes in free-hormone during pregnancy are controversial, though pregnant women in general have lower free-hormone concentrations at term than nonpregnant women (10,11).

Thyroglobulin frequently increases during pregnancy reflecting an enhanced activity of the thyroid gland (12).
The fetal thyroid begins concentrating iodine and synthesizing thyroid hormones after 12 weeks of gestation; before this time any request of thyroid hormones is supplied by maternal reserves, in order to promote the physiological fetal brain development (13,14).

Diagnostic accuracy and practical applicability

There is an unanimous consensus about the use of TSH, concerning the tests to be applied for diagnosis of thyroid dysfunction. This test is widely reproducible, reliable and not expensive, but evaluation of the results requires trimester specific reference ranges to not underestimate of hypothyroidism and overestimate of hyperthyroidism (15). This suggests that the upper limit for TSH should be 2.5 mIU/L in the first trimester, and 3.0 mIU/L in the second and third trimesters. Furthermore, the lower physiological limit could be 0.1 mIU/L in the first trimester, 0.2 mIU/L in the second, and 0.3 mIU/L in the third (16).
The presence of thyroid peroxidase antibody (TPOAb) permit to identify the woman at increased risk of developing thyroid disease, that must be submitted to check thyroid function once a trimester.
Serum FT4 measurement in pregnancy is conditioned by increased TBG and decreased albumin concentrations, that may affect the reliability of immunoassay measurement, so its application raises much discussion (17,18).

Hypothyroidism

Hypothyroidism is defined as a low FT4 levels with high TSH. The main cause is iodine deficiency, in areas where iodine intake is sufficient the most frequent cause is autoimmune thyroiditis. Other causes are prior thyroidectomy, radioiodine therapy, the use of drugs, congenital hypothyroidism, pituitary or hypothalamic disease, and immunoglobulin binding to the TSH receptor, blocking its activity. Hypothyroidism occurs in 2.5% of pregnancies (19,20); however, the frequency of OH is estimated to be between 0.2 and 1.0% (21,22).
Symptoms of hypothyroidism can often be masked by the hypermetabolic state of pregnancy.
In a retrospective study, Haddow et al. in 1999 first described reduced intelligence quotient (IQ) in babies born from hypothyroid mothers corroborating the association between hypothyroidism and increase risk of impaired neurodevelopment in the offspring (23).
The authors selected from 25,216 pregnant women 62 with serum TSH values above the 98th percentile in combination with low FT4 values and 124 matched women with normal values. Of these 62 women with thyroid deficiency, 48 were not treated for the condition during the pregnancy.
Their 7-9 year old children, none of whom had hypothyroidism as newborns, underwent 15 tests relating to intelligence, attention, language, reading ability, school performance, and visual-motor performance (Wechsler Intelligence Scale for Children, 3rd edition). The children of the 62 hypothyroid women revealed an IQ averaged 4 points lower than those of the children of the 124 matched control women (P = 0.06, not significant). Furthermore, 15% of the children of the affected mothers had IQ scores of 85 or less, compared with 5% of the matched control children born to euthyroid mothers. The full-scale IQ scores of their children averaged 7 points, significantly lower than those of the 124 matched control children (P = 0.005). The authors conclude that "undiagnosed hypothyroidism in pregnant women may adversely affect their fetuses; therefore screening for thyroid deficiency during pregnancy is warranted".
Several important obstetrical complications are the increased risk of spontaneous miscarriage, stillbirth and perinatal death. Other frequent complications are preterm delivery, fetal distress and increase in frequency of low birth weight infants (24-26), while the occurrence of gestational hypertension, placental abruption and postpartum hemorrhage have been shown to be increased in some, but not all, studies (27).
Abalovich et al. in 2002 demonstrated the fundamental importance of Levothyroxine (LT4) treatment to prevent fetal loss (incidence of 4% in adequate substitutive treated group versus 31% in inadequately treated group) (28).
Tan et al. in 2006 reported no increase in obstetrical and neonatal complications in treated hypothyroid women (29).
These results are validated by Negro et al. in 2010; they assessed adverse events in women with subclinical and overt hypothyroidism and saw that untreated thyroid dysfunction patients had a significantly higher rate of complications compared with those receiving treatment (30).
LT4 is the drug of choice for the treatment of hypothyroidism. In women affected before pregnancy, it's recommended to adjust the dose in order to have a pre-pregnancy TSH lower than 2.5 mIU/L and to maintain the same TSH level during the first trimester, and not exceed 3.0 mIU/L during the second and third trimester (31).
The LT4 dosage should be increased at beginning of pregnancy by 30-50%, and may be further increased during the second or the third trimester (32,33).
If hypothyroidism is diagnosed during pregnancy, it's crucial to restore euthyroidism as soon as possible (34).

Subclinical hypothyroidism

Subclinical hypothyroidism (SH) is defined as a normal FT4 levels with high TSH. SH is the most frequent thyroid disease occurring in pregnancy (7,21,22). The prevalence of SH varies between 1.5 and 4.0% from one study to another, depending on the definition of SH, ethnicity, iodine intake, and study design (35).
SH, as OH, causes several obstetrical complications (2,7). Findings from various studies, due to differences and limitations in study design and to an inadequate number of participants recruited, are unclear (26,28).
Allan et al., in 2000, demonstrated that pregnant women with TSH levels greater than 6.0 mIU/L had a significantly higher rate of fetal death than controls (3.8% vs 0.9%) (19).
Benhadi et al., in 2009, found a relationship between pregnancy loss and increased TSH values, with the incidence of child loss augmented by 60% for every doubling in TSH concentration (36).
In 2008 Cleary-Goldman et al. showed that complications

were associated with autoimmunity (37), while the study by Männistö et al. in 2009 found an association with thyroid autoimmunity, independent from thyroid function (38).
In another study, Negro et al. in 2010 showed an increased rate of pregnancy loss, 6.1 vs 3.6%, respectively, in women with TSH level between 2.5 and 5.0 mIU/L in the first trimester, compared with those having TSH levels less than 2.5 mIU/L and compared two strategies for detection and treatment (30).
The authors divided women affected by thyroid dysfunction in two groups, one treated with LT4 and the other left untreated. The results showed that untreated women had a significantly higher rate of complications compared with the treated.
A study, published by Lazarus JH et al. in 2012, examined women within the 16th week of pregnancy. Patients were assigned to a screening group, in which measurements of thyrotropin and FT4 were obtained immediately, or a control group, in which serum was stored and measurements were obtained shortly after delivery. TSH levels above the 97.5 centile and/or FT4 below the 2.5 centile were considered a positive screening result. Women with positive findings in the screening group were treated with 150 ∝g of levothyroxine per day. The results showed that there was no difference in IQ between the two groups, but the percentage of children with an IQ < 85 was higher in the untreated group compared with the treated group, even though non statistically significative (39).
Routine screening and treatment of subclinical hypothyroidism during pregnancy is not yet strictly recommended. National endocrinology organizations have greatly emphasized the need for large clinical trials to address this issue.

Management

Treatment of hypothyroidism should be initiated as soon as possibile. The starting dose of levothyroxine is 1-2 ∝g/kg/day and should be adjusted every 4 weeks. Women who are affected before pregnancy should increase their dose by approximately 30-50%. Levothyroxine requirements should increase as the pregnancy progresses, secondary to the greater demand for T4 with the progression of pregnancy as well as its inadequate intestinal absorption caused by ferrous sulfate replacement (33).

Follow-up after delivery

After delivery, levothyroxine dosage should be returned to the prepregnancy dose, and the TSH checked 6-8 weeks postpartum. Levothyroxine is excreted into breast milk, but levels are too low, so breastfeeding is not contraindicated.

Thyroid autoimmunity

Positivity for thyroid antibodies is quite a common finding in women of childbearing age, accounting around 10%, and represents the most common autoimmune disease. Stagnaro-Green et al. in 1990 published the first study that demonstrated an association between pregnancy loss and thyroid antibodies (40).
Evaluating the course of 550 pregnancies, they found that patients who were positive for Thyroglobulin antibodies (TgAb) or TPOAb had a 2-fold increase in the risk of pregnancy loss (17% vs 8.4%). In 2011 a meta-analysis considering 12,126 patients, found that women with thyroid antibodies had a 4-fold increased risk of miscarriage according to cohort studies, and a 1.8-fold increased risk according to case-control studies (41).
Glinoer et al. published the first report about the association of autoimmunity disease and preterm birth, subsequent studies found conflicting results (25). While Iijima et al. didn't find a significant association (42), Ghafoor et al. found that women with thyroid antibodies have a 4-fold risk of preterm delivery (43).
In a larger study, involved about 10,000 patients, conducted by Haddow et al., the association, although weak, was demonstrated (44). Also two meta-analyses confirmed a significant association with preterm birth, with an increased risk of 1.5-2-fold (41,45).
Negro et al. in 2006 carried out a prospective, randomized trial, recreuting 984 patients in the first trimester of pregnancy. Patients with thyroid autoimmunity, 11.7% of all patients, were divided into two groups, one of which was treated with levothyroxine (46). Results showed a significantly decreased rate of pregnancy loss (3.5% vs 13.8%) and a lower rate of preterm delivery in the treated group than the untreated group (22.4% vs 7%).
Several small non-randomized studies have been performed on the use of IVIG for the prevention of recurrent pregnancy loss in women with thyroid antibodies (47-49).
One reported a significant improvement in live birth compared with the control group (92% vs 0%), and another one, comparing levothyroxine with IVIG, showed a higher rate of term delivery in the group treated with levothyroxine. The available data on the use of levothyroxine or IVIG to prevent miscarriage rate have to be considered preliminary; although showed interesting results.

Hyperthyroidism

Hyperthyroidism is defined as an excessive production of thyroid hormones caused by immune or non immune thyroid disease. Hyperthyroidism is less common than hypothyroidism and interested only 0.2% of pregnancies. The normal physiological changes of pregnancy can hide some of the signs and symptoms.
Severe maternal hyperthyroidism is associated with increased risk of stillbirth, preterm delivery, intrauterine growth restriction, preeclampsia, and heart failure. Also, thyrotoxicosis at conception increases the risk for spontaneous abortion (50).
In most cases, the diagnosis is made for the first time during pregnancy. A goiter is almost always present and careful examination of the eyes may reveal signs of ophthalmopathy. During the first trimester of pregnancy, due to the additive effects of hCG stimulation on the TSH receptor, the symptoms suffer an exacerbation. In second half of pregnancy there is an improvement of symptoms, resulting in decreased requirements of antithyroid drug therapy (ADT) with progression of pregnancy (51-53).

The symptoms may worsen during the postpartum period (54,55).
Laboratory evaluation includes determination of serum TSH, FT4 and Thyroid Receptor Antibodies (TRAb) levels. High levels of TRAb cross placental barrier (56) and the risk of fetal and neonatal thyrotoxicosis increases with TSRAb values 3-5 times above normal (57,58).
The most common cause of non immune hyperthyroidism is "Transient Hyperthyroidism of Hyperemesis Gravidarum" (THHG), defined as transient hyperthyroidism, limited to the first trimester of pregnancy, characterized by elevated serum FT4 and suppressed or undetectable serum TSH, in the absence of thyroid autoimmunity (59).
Within 15 weeks, due to resolution of vomiting, serum FT4 normalized spontaneously; however, serum TSH may remain suppressed for others weeks and does not require ATD therapy (60). Occasionally the severity of symptoms requires ADT, as in the case of triple pregnancy (61).

Subclinical hyperthyroidism

Subclinical hyperthyroidism is defined as a serum TSH concentration below the lower limit of reference range, with FT4 and FT3 concentrations within normal reference range. It affects up to 1.7% of pregnant women. Subclinical hyperthyroidism in pregnancy has not been found to be associated with adverse outcomes (7).
The potential long-term adverse sequelae in the mothers suggests that these women may benefit from periodic surveillance later in life (26).

Management

The goal of treatment is to keep the patient euthyroid, using the lowest possible dose of antithyroid drugs necessary to maintain FT4 levels in the upper one-third of the normal non pregnant range or just above the normal range (62); excessive doses of ATDs, indeed, may affect fetal thyroid function, with the development of hypothyroidism and/or goiter (63,64).
The dose should be adjusted every 2-4 weeks and the presence of detectable TSH is an indication to decrease ATD dose (65).
The treatment of choise is propylthiouracil (PTU), but methimazole (MMI) is also an alternative, both are considered compatible with breastfeeding. PTU is given in a dose of 100-450 mg/day. It may be necessary 2-4 weeks from the start of treatment to see a clinical change. MMI can be prescribed at 10-20 mg/day. Beta blockers may be, also, used to control the adrenergic symptoms of thyrotoxicosis. In addition, beta blockers block the peripheral conversion of T4 to T3. Propranolol in a dose of 10-40 mg every 4-6 h or atenolol 25-50 mg daily, are recommended. In acute cases, intravenous esmolol (up to 200 ∝g/kg/minute) may be used to maintain a heart rate of less than 90 beats/min. Thyroidectomy is reserved for patients requiring high doses of medication or in the rare case of allergies to ATD (66).
The use of iodine therapy in addition to anti-thyroid medications has fallen into disuse due to higher rates of neonatal goiter and hypothyroidism (26). Radioactive iodine therapy is contraindicated in pregnancy and lactation. It is recommended to continue medications throughout the postpartum period (50,67).

Side effects of anti-thyroid drugs

Propylthiouracil (PTU), carbimazole (CBM) and methimazole (MMI) are equally efficacious to achieve euthyroidism. PTU shows a higher incidence of hepatotoxicity (68,69), whereas MMI has been associated with aplasia cutis and choanal/esophageal atresia, occurring with other congenital defects, including hearing loss, dysmorphic facial features, and developmental delay known collectively as "methimazole embryopathy" (70,71).
Rosenfeld et al., evaluating 115 PTU-exposed pregnancies with 1141 controls, concluded that PTU did not seem to be a major human teratogen (72).
In a recent study, Clementi et al. reported 3 cases of sinus inversus dextrocardia, 2 cases of isolated unilateral kidney a/dysgenesis and 5 cases of cardiac outflow tract defects in 47 subjects born to mothers with known first trimester PTU exposure; but further studies are required to evaluate these associations (73).
The present recommendation by the American Thyroid Association is to use PTU during the first trimester only, and to switch to MMI in the second and third trimesters (69).
Spontaneous abortion, gestational hypertension, premature delivery, low birth weight, placenta abruption, congestive heart failure and thyroid storms are the most serious complications, with incidence significantly increasing with poor control of the hyperthyroidism (65,74,75).
Millar et al., found that the risk of low birth weight infants was higher in uncontrolled women, compared with controlled women and healthy women (65).
Fetal and neonatal outcomes are affected by:
1) *Maternal TRAb levels;* the fetal thyroid gland is stimulated by TRAb crossing the placental barrier; high levels may induce fetal hyperthyroidism in some cases, with an incidence of 1-5% of all Graves' disease women (67,76). Signs of fetal hyperthyroidism are tachycardia, fetal growth retardation, fetal goiter, hydrops, and accelerated fetal bone maturation. At birth the fetus of mothers treated with ATD lost the ATD protective effect and neonatal hyperthyroidism may manifest in the first 72 h of life (77). Patients treated previously with thyroid ablation for Graves' hyperthyroidism, may have persistent elevations of TRAb, and, if not properly diagnosed, the fetus may developed hyperthyroidism. Treatment consists with starting dose of 10-20 mg MMI, adjusting the dose every few days (78).
2) *Maternal overtreatment with ATD;* it may produce fetal goiter and hypothyroidism. The diagnosis is suggested by the development of polyhydramnios. Intra amniotic administration of levothyroxine has been used with resolution of the goiter; however, discontinuation of ATD appears to be equally effective (79).
3) *Control of hyperthyroidism;* infants of untreated mothers affected by hyperthyroid may be born with congenital hypothyroidism of central origin, low serum T4 and inappropriately low TSH, probably caused by maternal T4 crossing the placenta barrier that suppressed fetal TSH (80).
Although recovery occurred in a few weeks after delivery, prolonged hypothyroidism with abnormal thyroid ultrasound patterns has been described (81).

Polak et al. evaluated the use of fetal ultrasonography, maternal serum TRAb and clinical history in 72 patients with past or present history of Graves' hyperthyroidism. In 11 fetuses, fetal goiter was detected, in 7 to excessive amount of ATD and in the other 4 due to high levels of TRAb in mothers receiving inappropriately low doses of ATD (58).

Postpartum care

During postpartum or within one year after delivery many patients may experience recurrent hyperthyroidism (82,83).
Thyroid function tests should be performed at regular intervals for the first year starting at 6 weeks postpartum (84).

Breastfeeding

Treatment with MMI during breastfeeding has been shown to not influence neonatal thyroid function; furthermore, physical and intellectual development at age 48-86 months remained unchanged compared with controls when assessed by the Wechsler and Goodenough tests (85).
The conclusion showed from these studies is that breastfeeding is safe during the use of ATD at moderate doses (PTU less than 150-200 mg/day or MMI10-20 mg/day). MMI is the drug of choice while breastfeeding.

Screening

The introduction of screening for thyroid dysfunction for all pregnant women is controversial.
The possibility of reducing the rate of adverse events is evident for overt thyroid disease, but less clear for subclinical one. In particular long-term potential benefits of treatment are also associated with the chance to minimize the risk of intellectual impairment in the offspring due to undiagnosed and untreated maternal hypothyroidism.
The potential negative effect of a screening strategy is mainly due to the chance of finding abnormal results. Another point of concern is the risk that healthy patients may be wrongly treated with anti-thyroid drugs by inexperienced clinicians (1).
The paucity of randomized prospective double blind placebo controlled trials, especially regarding subclinical hypothyroidism, makes difficult to find a unanimous consensus. Everyone agrees about the need to treat overt thyroid disease, while do not exists a consensus regarding the usefulness of treating subclinical hypothyroidism; just one prospective study has demonstrated a benefit in treating subclinical hypothyroid pregnant women, and these findings are yet to be confirmed (30).
Recently, two studies evaluated the cost-effectiveness of screening for thyroid function in pregnant women.
Dosiou et al., in the first study, compared three strategies: 1) no screening, 2) one time screening using anti-TPOAb, and 3) one time screening using TSH (86).
Screening using TSH results cost-saving compared with no screening; while screening using anti-TPOAb was cost-effective compared with TSH screening. Screening remained highly cost-effective in scenarios where no improvement of offspring IQ outcomes by levothyroxine treatment was assumed.
In the second study, Thung et al. developed a decision analysis model to compare the cost-effectiveness of no routine screening with routine screening of TSH levels (87).
Results showed that screening for SH was a cost-effective strategy.
In the absence of strong evidence that support universal thyroid screening in pregnancy, current guidelines suggest a case-finding approach targeting thyroid function testing in high-risk groups (88).
The case-finding strategy does not solve the serious problem of leaving undiagnosed and untreated patients without risk factors. From all the published studies, it is clear that by applying a case-finding strategy the majority of patients with thyroid dysfunction are missed. Negro et al., conducted one prospective randomized study compared the efficacy of universal screening with a case-finding strategy in detecting thyroid dysfunction. A total of 4562 pregnant women were randomized to universal screening or case-finding. The study confirmed that the case-finding strategy missed the majority of patients with thyroid dysfunction but universal screening compared with case finding didn't result in a decrease in adverse outcomes. Although treatment of hypothyroidism or hyperthyroidism identified by screening a low-risk group was associated with a lower rate of adverse outcomes (30).

Conclusion

It is well documented that thyroid disorders are associated with maternal and fetal complications during gestation and sequelea after delivery.
Despite the correlation between thyroid function during pregnancy and maternal and fetal outcomes is a widely discussed topic, it remains to clarify several points.
While ADT therapy does not appear to be relevant in patients with subclinical hyperthyroidism, in cases of overt hyperthyroidism it plays a key role.
In pregnant women with newly diagnose of overt hypothyroidism it is strongly recommended to begin substitutive treatment with LT4 as soon as possible, that should be considered in case of subclinical hypothyroidism; hypothyroid women already being treated by LT4 require an increase of dosage by 30-50% at the start of pregnancy.
In this review we tried to evaluate possible strategies to prevent and to apply appropriate management to avoid an unfavorable outcome for both mother and offspring.
However, further studies are needed to clarify the role of LT4 treatments in patients with subclinical hypothyroidism, and positive thyroid antibodies.

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