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Thyroid Dysfunction in Pregnancy – A Pandora's Box

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Abstract

Thyroid diseases affect upto 5% of all pregnancies. The repercussions of maternal thyroid dysfunction during pregnancy causes numerous maternal and fetal adverse outcomes just like the Pandora's box. Adequate treatment of these situations is thought to reduce the risks. Hypothyroidism is commonly treated with levothyroxine, with advancing pregnancy the levothyroxine requirement also increases. Hyperthyroidism is often treated with antithyroid drugs in pregnancy. However they are not completely safe to use during pregnancy but benefits of treatment with these drugs is found to outweigh the minor risks of side-effects. The treatment goal for hypothyroidism and hyperthyroidism is to achieve euthyroidism quickly and maintain it throughout pregnancy. Autoimmune thyroiditis and isolated maternal hyper-thyroxemia do not currently warrant treatment during pregnancy, unless hypothyroidism ensues. Treatment of thyroid nodules and differentiated thyroid cancer can generally be safely postponed until after delivery.

Keywords: Thyroid Dysfunction; Hyperthyroidism; Autoimmune Thyroiditis; Thyroid Hormone-Binding Globulin (TBG).

Introduction

Maternal thyroid function changes during pregnancy and inadequate adaptation to these changes results in thyroid dysfunction [1,2]. Some of these alterations occur due to thyroid hormone- binding globulin (TBG) concentration, increased iodine clearance in the kidneys and thyrotropic effect of human chorionic gonadotropin (hCG) [3,4]. Pregnancy can be considered as stress test of maternal thyroid function where woman with limited thyroid reserve may develop dysfunction [5]. Diagnosing thyroid diseases in pregnancy can be difficult as the clinical signs and symptoms mimic those of pregnancy. Hypothyroidism is associated with weight gain, fatigue, constipation while hyperthyroidism causes nausea and increased appetite [6,7]. Current recommendations suggest targeted TSH screening for women at high risk for thyroid disease before or during early pregnancy, with other thyroid function tests to confirm and grade the severity [5,8]. However, reference ranges of TSH or free thyroxin (fT_4) obtained from non-pregnant populations do not reflect normal values in pregnant women because of their physiologic changes in pregnancy [5,8]. Repeat laboratory sampling within a week is advisable in cases with isolated increases in TSH or decreases in fT_4 in pregnancy (especially in borderline values) to confirm diagnoses.

As diagnosing thyroid diseases during pregnancy may be difficult, adequate

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Table 1: Typical symptoms associated with hypothyroidism and hyperthyroidism

Hypothyroidism	Hyperthyroidism
Weight gain	Goiter
Constipation	Palpitations, Tremors
Fatigue	Heat intolerance
Muscle cramps, Muscle weakness	Weight loss
Intolerance to cold	Insomnia, Nervousness, Irritability
Dry skin, Hair loss	Frequent bowel movements
Voice changes	Eye symptoms

preconception diagnostics and management of thyroid diseases crucial. Pregnant women with thyroid diseases should be managed preferably in multidisciplinary clinics, where obstetricians, endocrinologists, paediatricians and other healthcare professionals can jointly work together to reduce risks of adverse pregnancy and neonatal outcomes associated with thyroid diseases.

Table 2: The current recommendations for targeted screening for women at high risk for thyroid dysfunction

The American thyroid association[5]	The Endocrine scociety[8]
Age 30 years / older	Age over 30 years
History of thyroid dysfunction and / or thyroid surgery	Family history of autoimmune thyroid disease or hypothyroidism
Family history of thyroid disease	Goiter
Goiter	Thyroid antibodies primarily (TPO-Ab)
Thyroid antibodies	Symptoms or signs of thyroid hypofunction
Symptoms and signs suggestive of hypothyroidism	Type 1 diabetes / other autoimmune disorders
Type 1 diabetes	History of miscarriage / preterm deliveries
Autoimmune disorders	Infertility
History of miscarriage / preterm delivery	Prior head / neck irradiation or prior surgery
Infertility	Current levothyroxine replacement
Prior head or neck radiation	Living in region with iodine deficiency
Morbid obesity	
Treated with amiodarone	
Recent exposure to iodinated radiological contrast agents (in past 6 weeks)	

Hypothyroidism

Hypothyroidism complicates upto 3% of pregnancies, of which 0.3 -0.5 % is overt and 2- 2.5% is subclinical hypothyroidism [5,8]. Overt and subclinical hypothyroidism as well as increases in maternal TSH concentrations have been associated with increase risk of miscarriages / fetal losses [9-16], hypertensive disorders of pregnancy [14,17-20], placental abruptions [18,21], preterm birth [15,16,21-24], and poor neurological development in the offspring [16,26,27].Overt hypothyroidism has also been associated with maternal anaemia and postpartum hemorrhage [18],and subclinical hypothyroidism with caesarean sections [14], gestational diabetes [21,27],breech presentation [28,29], infants being small for gestational age [15], fetal distress [26], neonates needing intensive care treatment [21,23], and respiratory distress syndrome [23]. Adequately treated hypothyroidism still appears to increase risk of cesarean sections but is not associated with other adverse outcomes [36].

Due to well established associations between overt hypothyroidism and adverse pregnancy outcomes, it should be promptly treated in an attempt to mitigate these known risk [5,8]. However, there is debate about whether to treat all women with subclinical hypothyroidism. Two different strategies are proposed: to treat everyone [8] or to treat women with positive thyroid antibodies [5]. In a study evaluating treatment for subclinical hypothyroidism, 44% of women with initially high TSH had normal thyroid function tests in a repeat sample taken 1 week later [37]. An ongoing randomised placebo controlled trail of levothyroxine treatment for subclinical hypothyroidism during pregnancy with early pregnancy sampling and longitudinal follow up will provide new information on natural history of untreated subclinical hypothyroidism and indicate whether levothyrorixne treatment is beneficial in reducing adverse outcomes.

Treatment of Hypothyroidism

Levthyroxine is treatment of choice in hypothyroidism with a goal of normalizing serum TSH levels, using the pregnancy specific refrence intervals [5]. In pregnancy treatment should be started with a dose as close to the final estimated dose as possible to minimise time with hypothyroidism [16]. Women with levothyroxine treatment should have preconception TSH levels less than 2.5mIu/l to minimise the probability of hypothyroidism during pregnancy [5]. However, even with adequate preconception management, upto 27% of women had elevated TSH concentrations in early pregnancy [38]. Therefore, the current recommendation is for women to increase their levothyroxine dose by 20 – 30% upon missed periods. Tighter control of hypothyroidism before pregnancy might reduce the risk of elevated TSH levels in pregnancy.

The etiology of thyroid disease also affects the need of levothyroxine dose adjustments in pregnancy. Women with post ablative or surgical hypothyroidism require higher dose increases than those with primary hypothyroidism or thyroid cancer, irrespective of good baseline management of hypothyroidism [39]. An individualised approach based on baseline TSH concentrations and etiology of hypothyroidism could

be utilised when counselling women treated with levothyroxine who are planning pregnancy, as lower baseline TSH levels could potentially reduce the risk of TSH elevations during pregnancy. Given that pregnant women are at increased risk of TSH elevations, tests for thyroid function should begin in early pregnancy, continuing every 4 weeks until mid-gestation and at least once between 26 and 32 weeks among those with levothyroxine treatment to ensure euthyroidism throughout pregnancy [5,8]. Newly diagnosed overt hypothyroidism in pregnancy require almost double the dose of levothyroxine compared to those treated for subclinical hypothyroidism [40]. Either weight based starting dose or a steady starting dose based on the severity of newly diagnosed hypothyroidism determined by baseline TSH concentration seem to be appropriate in reaching euthyroidism.

In a systematic review, treatment of clinical hypothyroidism was shown to reduce risk of miscarriage and preterm birth [41]. There is currently insufficient evidence to show clear benefits of treating subclinical hypothyroidism [42]. Among women undergoing assisted reproduction, levothyroxine treatment of subclinical hypothyroidism has been shown to reduce miscarriages at least in some cases [42], if not all [43].

Only about 62-82% ofall ingested levothyroxine is absorbed, with concurrent ingestion of food, caffeine and iron and calcium supplements decreasing the absorption further [44]. Levothyroxine should be ingested in the morning at least 60 minutes before eating [44]. Additionally, there should be a 4 to 6 hours gap between levothyroxine ingestion and administration of other medications that decrease levothyroxine absorption [44]. In addition several chronic conditions including celiac disease, lactose intolerance and atrophic gastritis decrease levothyroxine absorption if untreated [44]. Compliance with medication as well as gastrointestinal conditions and medication interference should be evaluated in women with persistent hypothyroidism requiring higher than normal doses of levothyroxine [44]. Different levothyroxine products are not clinically interchangeable and there might be more than 12.5% difference in levothyroxine doses between products [45,46]. For optimised therapy, patients are often advised to stay on the same brand of levothyroxine. If products are switched, thyroid function tests should be performed to ensure euthyroidism [46]. Staying under the same brand might be especially crucial in pregnancy where adverse effects of hypothyroidism are well established.

Most women with hypothyroidism can reduce their dose of levothyroxine postpartum, with assessment of TSH levels 6 weeks following the dose reduction to ensure euthyroidism [5]. Women with positive thyroid antibodies are at higher risk of exacerbation of autoimmune thyroid dysfunction postpartum, and over 50% of women with Hashimoto's thyroiditis continued to require doses of levothyroxine in postpartum period [47]. Women with subclinical hypothyroidism during pregnancy may not require treatment during the postpartum period, unless postpartum thyroiditis ensues or the women is planning to conceive again soon. These women are at high risk for thyroid dysfunction in their subsequent pregnancies and require adequate preconception consultation and management. They are also at higher risk of developing permanent thyroid disease later in life [32].

Hyperthyroidism

Hyperthyroidism develop in 0.1 -1% of all pregnancies and is diagnosed when TSH concentrations are low or suppressed along with elevated free fT_4 or triiodothyronine (in overt disease) or with normal thyroid hormone levels (in subclinical disease) [5]. Grave's disease an autoimmune condition characterised by stimulation of the thyroid glands by TSH receptor antibodies (TRAbs), is the most common cause of hyperthyroidism among fertile-aged women. Other reasons include toxic multinodular goiter, toxic adenoma, thyroiditis or struma ovarii. As untreated Grave's disease can lead to ovulatory dysfunction and infertility, a new onset of Grave's is thought to be rare in pregnancy. A more common condition gestational (transient) hyperthyroidism occurs in up to 1-3% of all pregnancies and is probably due to the physiologic thyroidal stimulation by high hCG levels in early pregnancy [5,8]. Notably, up to 50% of women with hyperemesis gravidarum (severe nausea and vomiting in early pregnancy) have transient hyperthyroidism.

Distinguishing between new-onset or recurring Grave's disease in pregnancy and gestational hyperthyroidism may be difficult. Symptoms associated with Grave's disease (goiter or eye symptoms) as well as previous history of thyroid disease help in differentiating between Grave's disease and transient hyperthyroidism, gestational hyperthyroidism is more common among women without history of thyroid disease [5,8]. Elevated TRAb titers are rarely present in gestational hyperthyroidism, so their presence can help confirm Grave's disease in pregnancy [5,8].

Hyperthyroidism is associated with increased risk of pregnancy complications, including miscarriages,

preeclampsia [48], low birth weight or fetal growth restriction [48],and maternal cardiac dysfunction [49], with risks increasing with poor hypothyroidism control [48]. However, even in populations with treated hyperthyroidism, the risks of some neonatal outcomes seemed to be higher [50,51]. However, gestational hyperthyroidism has not been associated with adverse pregnancy outcomes [5,35,36].

Treatment of Hyperthyroidism in Pregnancy

As the associations between untreated persistent hyperthyroidism and adverse pregnancy outcomes are well established, hyperthyroidism should be adequately managed before and during pregnancy [5,8]. In non-pregnant patients, the management options for Graves' disease include radioactive iodine ablation, anti thyroid drug treatment and / or surgery [6]. Whereas only anti thyroid drugs and surgery are options in pregnant patient [5,8]. Radioactive iodine ablation results in long latency of 2-6 months before development of hypothyroidism as well as in an increase in TRAb titres. As such, this treatment option is not generally recommended for hyperthyroid women planning pregnancy in near future (within 6 months of the treatment) as it is unlikely to achieve stable euthyroid state during that time [5,6]. Surgery is an option for patients hoping to conceive soon after the operation, but even then, the optimal management of hypothyroidism after total or near total thyroidectomy should be reached before conception to reduce risks of adverse pregnancy outcomes [5,6].

In non-pregnant women with hyperthyroidism, antithyroid drugs are often recommended as these patients have high likelihood of remission [6]. Notably, upto 30% of patients with Graves' disease may achieve remission without treatment [6]. Generally antithyroid drugs are used in non-pregnant patients for up to 12 – 18 months, after which they are discontinued if TSH is normal at that time. Women who have achieved remission of hyperthyroidism before pregnancy with antithyroid drug therapy seem to have a low risk of hyperthyroidism relapse during pregnancy but a high relapse risk postpartum [6]. Still such women with history of treated hyperthyroidism need to be carefully monitored during pregnancy for clinical or biochemical signs of relapse as well as to be tested for TRAb positivity at mid – gestation [5].

Antithyroid drugs can also be used to control hyperthyroidism in women planning pregnancy or among those with newly discovered Graves' disease during pregnancy [5,8]. The antithyroid drugs methimezole (and it's prodrug carbimazole) is associated with teratogenicity, including aplasia cutis and choanal atresia and esophageal atresia [53]. However, these specific malformations are very rare on a population level. The other commonly used antithyroid drug, propylthyiouracil, is not associated with teatogenicity butin rare instances propylthiouracil may increase the risk of hepatotoxicity in the mother. Current recommendations suggest using propyltiouracil during preconception and in the first trimester of pregnancy to reduce tertogenicity in and switching to methimazole in later pregnancy to avoid hepatotoxity [5,8]. However, if one antithyroid drug is not available or there are tolerance issuses, either propylthiouracil or methimazole can be used throughout pregnancy as the neonatal and maternal risks of untreated maternal hyperthyroidism outweigh the small risks of malformations or liver toxicity [5,8].

Both anti thyroid drugs have been found to be similarly effective in treating hyperthyroidism [5,8]. After switching between products, thyroid function should be promptly tested (within 2 weeks) with a subsequent follow up every 4-6 weeks once euthyroid state is reached. Surgery is also an option for pregnant patients where rapid control of hyperthyroidism is required or antithyroid drugs cannot be used.[6] However anaesthetic agents are teratogenic in the first trimester and surgery is associated with increased fetal loss in the third trimester, the late second trimester is thought to be the safest period to perform thyroidectomy in a pregnant woman [6]. Women with gestational hyperthyroidism generally do not require treatment as the condition is transient and not associated with adverse outcomes [5,31,32]. Propranolol, a beta blocker, can be used in short-term symptom management as it has some direct antithyroid activity by blocking iodide transport to the thyroid. However, if women do not reach euthyroidism as pregnancy progresses or there are other symptoms, Graves' disease should be suspected and a treatment trail with antithyroid drugs may be useful [5].

All antithyroid drugs cross placenta and may have deleterious impacts on the fetal thyroid function. When treating pregnant women with antithyroid drugs the treatment goal is to maintain fT4 values at or above the upper non-pregnant reference limit or high normal within the pregnant reference limit (preferred approach) using the lowest possible dose of the drug [5]. Besides the fetal hypothyroidism risk inflicted by maternal antithyroid drug therapy, untreated maternal hyperthyroidism may lead to transient central hypothyroidism in the fetus [5]. Fetal survelliance with serial ultrasound is required to

diagnose fetal thyroid dysfunction and follow fetal growth and wellbeing if a woman has uncontrolled hyperthyroidism and/or positive TRAb during pregnancy. Levothyroxine and antithyroid drugs should not be used together, except in the rare cases of fetal hyperthyroidism. Administering both concurrently leads to a relative increase in maternal fT4 levels leadingto increased requirements of antithyroid drugs, which in turn may lead to fetal hypothyroidism [5]. Women with a history of Grave's disease or hyperthyroidism treated during pregnancy are at higher risk of relapse during the postpartum period [5]. Moderate use of antithyroid drugs is safe during lactation and has not been shown to affect thyroid hormone levels or the development of the infant. However, as a safety precaution, infants of mothers taking antithyroid drug during lactation need to be followed with thyroid function tests and antithyroid drugs should be taken in divided does immediately after feeding [5].

Autoimmune Thyroiditis and Postpartum Thyroiditis

Approximately 11–15 % of all fertile women have positive thyroid antibodies, either thyroid peroxidase antibodies (TPO-Abs)or thyroglobulin antibodies (TG-Abs), which act as marker of silent autoimmune thyroiditis. Up to 20–40 % of all women with positive thyroid antibodies develop hypothyroidism during pregnancy or immediately postpartum [53,54], and generally women with autoimmune thyroiditis have higher TSH concentrations at baseline [54]. Notably, TPO-Ab and TG-Ab concentrations decrease as pregnancy progresses [54], so false negative findings regarding thyroid autoimmunity are possible in late gestation.

Thyroid antibody positivity has been associated with increase risk for miscarriages [55-58], perinatal mortality [31], and preterm birth [57]. TPO-Ab positivity in euthyroid women is associated with placental abruptions [59], very early preterm delivery [60], neonatal respiratory distress [60], and externalising problems, for example, attention problems and aggressive behaviour, in children [61]. However most of these studies have evaluated thyroid function only once during pregnancy, so the effect of hypothyroidism as the underlying reason for these associations cannot be ruled out.

Postpartum thyroiditis is a new onset thyroid dysfunction during the 12 months following pregnancy in a previously euthyroid woman [5]. The risk of postpartum thyroiditis is higher in women with positive thyroid antibodies or other autoimmune diseases . Up to 50% of all women with TPO-Ab or TG-Ab positivity in first trimester of pregnancy develop postpartum thyroiditis. In its classical form, postpartum thyroiditis manifests with an episode of thyrotoxicosis followed by transient hypothyroidism and subsequent euthyroidism but the clinical course varies [5,63]. The thyrotoxic phase generally does not require or respond to antityroid drugs but symptomatic women may be treated with a low dose of proprnanol. Treatment of the hypothyroid phase of postpartum thyroiditis with levothyroxine depends on the symptom severity, if a woman is breastfeeding, if she plans to conceive again in the near future and her prefrence to receive treatment [5,63]. Treatment for postpartum thyroiditis is usually transient, with discontinuation of treatment 6-12 months after the initiation, unless the patient is pregnant, breastfeeding or trying to become pregnant [5,63]. Postpartum thyroiditis can lead to permanent hypothyroidism in over 50% of all women and annual TSH tests are indicated to those with postpartum thyroiditis history [5,63].

Thyroid Nodules & Thyroid Cancer

Thyroid size increases during pregnancy and pregnancy has been considered to be a risk factor for increasing growth of thyroid nodules [5]. However, it is still unclear that thyroid nodules are commonly diagnosed in pregnant than in non-pregnant women, although radionuclide scans are contraindicated in pregnancy [5]. Upon discovering the thyroid nodules , a complete family and personal history and clinical examination, including thyroid function tests should be performed [5,62]. Thyroid ultrasound is an accurate diagnostic tool that can be used in pregnancy to help determine the features and growth of nodules. Fine-needle aspiration biopsy is another safe procedure during pregnancy and pregnancy does not have an effect on its diagnostic accuracy [5].

Women diagnosed with differentiated with differentiated thyroid cancer during pregnancy seem to have a similar prognosis if surgery is performed during or after pregnancy [5,62]. Therefore, surgery for differentiated thyroid cancer can generally be delayed until after delivery , although sonographic monitoring over the course of pregnancy is indicated [5,62]. Thyroid hormone suppression therapy may be considered for these patients, with goal of reducing TSH to 0.1-1.5 mU/l [5,62]. If surgery is required due to thyroid cancer, the safest time to perform surgery is in the second trimester [5,62]. Benign thyroid nodules do not generally require treatment during pregnancy, unless compressive symptoms develop or if there is rapid growth [5,62].

Women with thyroid cancer in remission on suppressive thyroid hormone therapy should

continue this treatment throughout pregnancy, as subclinical hypothyroidism does not seem to affect pregnancy outcomes [5,31,32]. Thyroid cancer patients generally also require increases in levothyroxine doses during pregnancy to reach these goals, but the dose increases are usually smaller than among those with primary hypothyroidism [31]. Thyroid function tests should be conductedevery 4-6 weeks in pregnancy to ensure that treatment goals are met [5].

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