Review Article

Think Thyroid - Think Life: Pregnancy with Thyroid Disorders

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Abstract

Thyroid dysfunction is a common problem encountered during pregnancy in clinical practice. There is good evidence that treatment of overt thyroid dysfunction negates risk imparted to both the mother and fetus. Clinical data on the treatment of subclinical disease is evolving and remains a topic of discussion. Various societies have published guidelines on the management of thyroid disease during pregnancy. Thyroid Stimulating Hormone (TSH) remains the most reliable test during pregnancy. Interpretation of thyroid function in pregnancy depends on the accurate knowledge of the stage of pregnancy and if available trimester specific reference ranges in that particular population. The most common cause of hypothyroidism during pregnancy is chronic autoimmune thyroiditis. Overt Hypothyroidism is associated with increased risk of several complications including preeclampsia, pre-term delivery, low birth weight, increased risk of caesarean section, peri-natal morbidity and mortality, postpartum hemorrhage and possible neuropsychological and cognitive impairment. In patients with pre - existing hypothyroidism, an increased requirement of thyroxine around 25-50 % may be needed during the first and second trimester of pregnancy. Untreated or sub - optimally managed maternal hyperthyroidism has been associated with preterm delivery, recurrent fetal loss, and low birth weight, pre-eclampsia and high risk of heart failure. Anti-thyroid medications Propylthiouraacil and Carbimazole remain the main mode of treatment. The most important factor in the management of thyroid disease in pregnancy is to consider normal physiology in pregnancy before considering treatment.

Key Words: Thyroid, Pregnancy, Hypothyroidism, Hyperthyroidism, Grave's disease, Sub - clinical hypothyroidism, Hyperemesis gravidarum

Introduction

Thyroid dysfunction is one of the most common endocrine disorders encountered during pregnancy[1]. Overt thyroid dysfunction is prevalent in up to one percent of all pregnancies. Untreated or sub - optimal management of thyroid dysfunction can cause serious consequences both for the mother and the fetus. There is good clinical evidence, which demonstrates that treatment of overt thyroid disease negates most adverse outcomes. Subclinical thyroid dysfunction is more widely prevalent and the prevalence varies in different populations. Treatment for sub-clinical disease in pregnancy is evolving and remains a hot topic of discussion. Universal screening for thyroid dysfunction in pregnancy remains controversial. Various professional societies have reviewed the available clinical evidence and published guidelines on the management of thyroid disease in pregnancy[2-4]. In this clinical review we review the current evidence for screening and management of both overt and subclinical thyroid disease in pregnancy.

Physiological changes associated with pregnancy

A normal pregnancy results in a number of physiological changes, to meet for the increased metabolic changes during pregnancy. The two major changes in thyroid function are the increasing thyroid binding globulin (TBG) concentrations and stimulation of the Thyroid stimulating hormone (TSH) receptor by human chorionic gonadotrophin (hCG) during the first trimester. During pregnancy, serum TBG concentration increases up to twice the normal level due to increase in estrogen and decreased clearance of TBG due to sialylation[5]. The thyroid gland in turn has to produce more Thyroxine (T_4) and Triiodothyronine (T_3) to maintain satisfactory free hormone levels for both the mother and the fetus. The total T_4 and T_3 hormone concentrations rise during the first trimester of pregnancy and reaching steady state levels around 20 weeks. The second major change to thyroid function occurs during the first trimester of pregnancy due to the stimulatory effects of hCG on the TSH receptor.

Serum HCG concentrations starts to increase soon after fertilization and peaks around 12 weeks of pregnancy. HCG belongs to a family of glycoprotein hormones and is made of 2 sub-units. It shares a common alpha sub-unit with TSH and has a unique beta-subunit. Due to this close homology with TSH, HCG exhibits a stimulatory activity over the TSH receptor causing mild hyperthyroidism between 10-12 weeks when HCG activity is at its peak. During this period, Serum total T4 and T3 concentrations increase with minor increase in free thyroid hormone levels. This is mirrored by appropriate reduction in TSH. In a small proportion of women the TSH may be low or even become undetectable. This suppression is always proportional to the HCG peak between 10 – 12 weeks gestation and is transient and physiological. The HCG starts declining at the end of first trimester, free hormones start to normalize and TSH rises back to normal by 16-20 weeks of gestation[6].

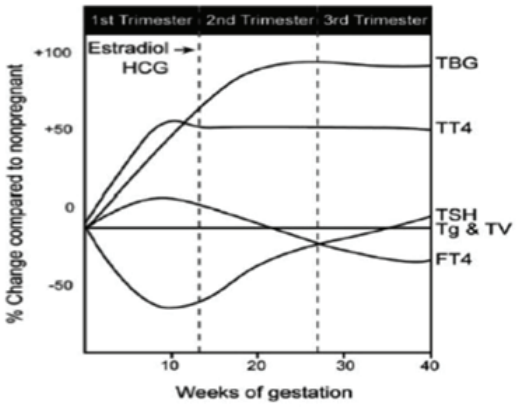

Fig 1 : Thyroid hormonal changes in Pregnancy Adapted from Glinoer et al. 1997 Ref:1

Physiologic Change	Thyroid-Related Consequences
↑ Serum thyroxine-binding globulin	↑ Total T4 and T3; ↑ T4 production
↑ Plasma volume	↑ T4 and T3 pool size; ↑ T4 production; ↑cardiac output
D3 expression in placenta and (?) uterus	↑ T4 production
First trimester ↑in hCG	↑ Free T4; ↑ basal thyrotropin; ↑ T4 production
↑ Renal I- clearance	↑ Iodine requirements
↑T4 production; fetal T4 synthesis during second and third trimesters	
↑ Oxygen consumption by feto-placental unit, gravid uterus, and mother	↑ Basal metabolic rate; ↑ cardiac output

Table 1: Normal thyroid physiology and pregnancy
Glinoer D, De NP, Bourdoux P et al. Regulation of maternal thyroid during pregnancy. J. Clin. Endocrinol. Metab. 71(2), 276–287 (1990).

Normal range of TSH in Pregnancy

Thyroid dysfunction has to be diagnosed in pregnancy by a thyroid function test due to indistinguishable symptoms of pregnancy as well as the asymptomatic nature of sub-clinical thyroid disease. The serum TSH concentration is the most reliable test during pregnancy. The American thyroid association has recommended using trimester specific reference ranges for TSH during pregnancy. If these ranges are not provided by the laboratory, the following reference ranges can be used: first trimester, 0.1 – 2.5 mIU/L; second trimester, 0.2 – 3.0 mIU/L and third trimester, 0.3 – 3.0 mIU/L[2,7,8]. The correct interpretation of thyroid function in pregnancy requires the accurate knowledge of the woman's gestational age and if available the appropriate population–based reference interval.

Hypothyroidism complicating Pregnancy

The most common cause of hypothyroidism during pregnancy is chronic autoimmune thyroiditis, provided iodine insufficiency is not prevalent in the population. In iodine insufficient areas, iodine deficiency can be a cause for goiter and hypothyroidism. Other rare causes are drugs including anti-thyroid medications, pituitary disorders, prior radioiodine treatment and previous thyroid surgery. Untreated or sub-optimal treatment of hypothyroidism can cause adverse effects both to the mother and fetus. Overt Hypothyroidism is associated with increased risk of several complications including preeclampsia, pre-term delivery, low birth weight, increased risk of cesarean section, peri-natal morbidity and mortality, postpartum hemorrhage and possible neuropsychological and cognitive impairment[9]. The prevalence of overt hypothyroidism has been estimated to 0.3 – 0.5 %[10].

Subclinical hypothyroidism is more common than overt hypothyroidism and the risk of complications are proportional to the severity of hypothyroidism. Early studies have estimated the prevalence of subclinical disease around 2.5 %, however recent estimates using the new criteria have reported prevalence as high as 27 %. Ablavich et al showed about 60% risk of fetal loss with untreated or less than optimally treated hypothyroidism[11,12]. Leung et al found a 22% increased risk of gestational hypertension when compared to controls [13]. Overt maternal hypothyroidism is associated with neonatal neurologic developmental delay because of inadequate transfer of thyroid hormones to the fetus. The fetus is totally dependent on maternal thyroxine levels because the fetal thyroid starts to function only around 12 - 14 weeks of gestation. Untreated hypothyroidism is also associated with increased risk of fetal death. A large randomized trial over 4500 women in the first trimester of pregnancy were assigned to universal screening or case finding groups[14]. All patients in the universal screening group and high-risk patients in the case finding group were tested for thyroid function and ATPO antibodies in the first trimester. Patients were treated if they had positive ATPO antibodies and an increased TSH of > 2.5 mIU/l. The low-risk women in the universal screening group found to have sub-clinical hypothyroidism, TSH >2.5 and positive antibody titres, who underwent treatment had a lower risk of miscarriage, pre-eclampsia, gestational diabetes and pre-term labor. But this study failed to show any advantage of the universal screening strategy when compared to a case finding strategy [14].

Universal screening for asymptomatic pregnant women for hypothyroidism during the first trimester remains controversial. Because of insufficient evidence for universal TSH screening, most professional societies including the American Thyroid Association (ATA), The Endocrine society and the American College of Obstetricians and Gynecologists (ACOG) recommend targeted case finding than universal screening. The ATA recommends testing only if an individual has a positive family history of thyroid disease, TPO antibodies, type 1 diabetes, history of preterm delivery or miscarriage, head and neck radiation, infertility, morbid obesity, from an area of iodine insufficiency or age > 30 years. In women who fulfill the screening criteria, TSH can be measured in the first trimester and if it is greater than 2.5 mIU/L, free T4 estimation can be done to estimate the degree of hypothyroidism. In these women the risk could be further assessed by checking for anti - thyroid peroxidase (ATPO) antibodies [15,16].

Hyperthyroidism complicating Pregnancy

Overt Hyperthyroidism can adversely affect the mother and the fetus, depending on the severity of the disease. Untreated or sub - optimally managed maternal hyperthyroidism has been associated with preterm delivery, recurrent fetal loss, and low birth weight, pre-eclampsia and high risk of heart failure. Overt thyrotoxicosis occurs in 0.2 – 0.4 % of all pregnancies and the diagnosis is based on suppressed TSH with elevated free T4 and free T3 levels [2,3,17]. The most common cause of hyperthyroidism in pregnancy is Grave's disease. Gestational thyrotoxicosis is also a frequent occurrence in the first trimester and may be present in up to 3% of all pregnancies. This is a transient phenomenon and it is important to differentiate the same from Grave's hyperthyroidism hence unwarranted treatment may be prevented as levels spontaneously return to normal around 14 – 18 weeks gestation[18,19].

Grave's disease in pregnancy

Grave's disease is diagnosed when there is a history of pre-existing thyroid disease, presence of goiter, thyroid-related ophthalmopathy or the presence of TSH receptor antibody (TRAb). The goal of hyperthyroidism treatment is to maintain serum free T4 concentration in the upper normal range. The dose of anti-thyroid medications should be titrated depending on serum free T4 and TSH measurements undertaken every 4 weeks with regular clinical assessment. Once euthyroid status is achieved, the anti-thyroid drugs (ATD) dose should be titrated down actively and maintained at the lowest dose required to maintain euthyroidism. When thyroid function becomes stable less frequent monitoring, every 6 to 8 weeks is sufficient.

The most common ATDs used in pregnancy are Propylthiouracil (PTU) and Carbimazole (CBZ) to minimize adverse outcomes. However, the use of these drugs are associated with birth defects like aplasia cutis, choanal atresia or esophageal atresia in a small but significant proportion of exposed children[20,21]. Propylthiouracil is the preferred ATD of choice in the first trimester since placental transfer of PTU is significantly less compared to Carbimazole. However, since the concern of hepatotoxity with PTU, most professional societies have advised usage of Carbimazole in the second and third trimester of pregnancy[22]. The natural course of Grave's hyperthyroidism gradually improves in late stages of pregnancy and some women will need reduction of medications in the second and third trimester. Beta-blockers may be used in patients who are troubled by severe hyper metabolic symptoms due to hyperthyroidism. It is better to stop beta-blockers after a few weeks since long-term use of Beta-blockers is associated with intrauterine growth retardation, fetal bradycardia and neonatal hypoglycemia[23]. Radioctive iodine therapy and functional nuclear imaging are contraindicated in pregnancy. Surgery can be rarely performed in the second trimester if euthyroid status is not possible using current medical strategies.

Neonatal Thyrotoxicosis

One percent of newborns born to women with Grave's disease have hyperthyroidism due to trans-placental transfer of TSH receptor stimulating antibodies. High levels of maternal TRAb had been associated with fetal hyperthyroidism. A maternal TRAb test performed between 24-28 weeks of gestation is a good predictor of impending thyrotoxicosis in the neonatal period[24,25]. Fetal tachycardia, growth restriction, accelerated bone maturation; heart failure or hydrops are suspicious findings suggestive of fetal hyperthyroidism [26].When present at birth, most of neonatal hyperthyroidism is self - limiting. If treatment becomes necessary PTU,

propranolol and prednisolone could be used. If TRAB levels are very high in the 3rd trimester, treatment of the mother with PTU enables the drug to cross through the placenta to protect fetus. Rarely the child develops his or her own TSH receptor antibody and present with hyperthyroidism around 3-6 months. Most of these infants invariably have a very strong family history of Grave's disease and carry a risk of 20% mortality and persistent brain dysfunction.

Hyperemesis gravidarum

It is a syndrome of severe nausea and vomiting leading to at least 5% loss of body weight, dehydration, and ketosis. It occurs in around 0.1 - 0.2 percent of pregnancies. And these women have higher serum HCG and estradiol concentrations than normal pregnant women. The absence of goiter, ophthalmopathy, absence of the common symptoms and signs of hyperthyroidism and the presence of vomiting can differentiate it from Grave's disease [27]. 60% of these women have a subnormal serum TSH level (< 0.4 mU/L) and another 50% have an elevated serum free T4 concentration. Severity of the vomiting is positively correlated with maternal free T4 levels but not to thyroid function. This is most likely to be due to HCG stimulation of the thyroid gland. This does not require any active treatment but for supportive care until normalization of free T4 levels, which happens by mid-gestation[19,27].

Postpartum thyroiditis

Postpartum thyroiditis is a destructive thyroiditis due to autoimmune mechanism within one year of delivery. It can present as transient hyperthyroidism, transient hypothyroidism or hyperthyroidism followed by hypothyroidism[18]. The reported prevalence varies from 1-17 % globally but the mean prevalence rates are approximately around 7 - 8 percent. Very high prevalence is noted in patients with Type 1 Diabetes, previous post-partum thyroiditis and positive anti-thyroid peroxidase antibodies. In one particular study when patients were followed up for a period of around 8 years, one third developed permanent hypothyroidism[28,29]. The biochemical and clinical features are very similar to patients suffering from painless autoimmune thyroiditis. Radioiodine uptake scan may show a poor or very low uptake during the hyperthyroid phase. Nuclear imaging is a relative contraindication for breastfeeding and feeding the baby should be avoided for at least 1 week.

Conclusion

Knowledge regarding maternal thyroid disease during pregnancy has increased tremendously over the last decade. Overt maternal thyroid dysfunction is associated with increased risk of adverse outcomes during pregnancy and appropriate treatment abates risk. The debate continues with regards to, if treatment of sub-clinical thyroid dysfunction improves outcomes in the mother and the newborn. The current data available are mostly from observational studies with cross-sectional thyroid function testing with indecisive results. Data from prospective longitudinal randomized controlled trails are the need of the hour in the management of sub-clinical thyroid disease in pregnancy. With the current evidence available, one has to consider normal physiology and its variations during pregnancy before considering treatment.

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