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HYPERTHYROIDISM IN PREGNANCY –A REVIEW

General Surgery

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ABSTRACT

Hyperthyroidism in pregnancy leads to a lot of complication in mother as well as in foetus..Hyperthyroidism in women who are of childbearing age is predominantly of autoimmune origin and caused by Graves' disease.Graves' hyperthyroidism affects 0.2% of pregnant women.The physiological changes in the maternal immune system during a pregnancy may influence the development of this and other autoimmune diseases. Furthermore, pregnancy-associated physiological changes influence the synthesis and metabolism of thyroid hormones and challenge the interpretation of thyroid function tests in pregnancy. Thyroid hormones are crucial regulators of early development and play an important role in the maintenance of a normal pregnancy and in the development of the fetus, particularly the fetal brain. Untreated or inadequately treated hyperthyroidism is associated with pregnancy complications and may even program the fetus to long-term development of disease. Pregnant women with hyperthyroidism need careful management as some may be at increased risk of fetal loss, pre-eclampsia,heart failure, premature labour, and having a low birthweight baby. Hyperthyroidism in pregnant women should be carefully managed and controlled, and proper management involves different medical specialties. The treatment of choice in pregnancy is antithyroid drugs (ATDs).

KEYWORDS

Thyroid, Hyperthyroidism, Graves' Disease, Pregnancy, Antithyroid Drug, Fetal Programming.

INTRODUCTION

Hyperthyroidism is defined by abnormally high levels of thyroid hormone caused by an increased synthesis and secretion of thyroid hormone from the thyroid gland.[1] The term "thyrotoxicosis", on the other hand, is used to describe "excess of thyroid hormone", and this can be due to an increased synthesis of thyroid hormone in the thyroid gland (hyperthyroidism), but may also occur in the absence of hyperthyroidism, eg, in patients with leakage of thyroid hormone from the thyroid gland (thyroiditis) or in patients with excess intake of thyroid hormone.[15] Hyperthyroidism in pregnancy is a special clinical situation because physiological changes related to the pregnant state challenge the interpretation of thyroid function test and because potential complications related to the disease and/or the treatment may compromise the health of the pregnant woman and also the developing fetus.[4,5]Hyperthyroidism can be overt (suppressed thyroid-stimulating hormone [TSH] and elevated T3 [triiodothyronine] and/or T4 [tetraiodothyronine] in a blood sample) or subclinical (suppressed TSH and normal T3 and T4).[2,]

Etiology of hyperthyroidism

Overt hyperthyroidism can be divided into different subtypes from the underlying etiology.The three most common subtypes are Graves' disease, multi nodular toxic goiter, and solitary toxic adenoma.

Causes of thyrotoxicosis

Group	Disease	Relative frequency
Thyrotoxicosis of thyroid origin	Grave's disease	70%
	Toxic adenoma	5%
	Multinodular toxic goitre	20%
	Iodine induced thyrotoxicosis	<1%
	TSH secreting adenoma	<1%
	Neonatal thyrotoxicosis	<1%
Associated with thyroid destruction	Subacute thyroiditis	3%
	Silent thyroiditis	3%
	Amiodaron -induced thyrotoxicosis(type 2)	<1%
Thyrotoxicosis of non-thyroid origin	Factitious thyrotoxicosis	Very rare
	Thyroid hormone poisoning	Very rare
	Struma ovari	Very rare
	Metastatic thyroid cancer	Very rare

Graves' disease is an autoimmune disease in which hyperthyroidism is caused by the production of autoantibodies that are directed against the TSH receptor and stimulate the thyroid gland to an increased production of thyroid hormone.[1] Biochemically, increased serum levels of TSH receptor antibodies (TRAb) are detectable in 95% of patients with Graves' disease.[7] Hyperthyroidism caused by multinodular toxic goiter or toxic solitary adenoma is not considered of autoimmune origin, but develops from thyroid autonomy, where the synthesis of thyroid hormone occurs independently of regulation by TSH.[8] Such thyroid autonomy is often seen as a late consequence of iodine deficiency.

Physiological changes in the pregnant state affect the function of the thyroid gland. The steep increase in human chorionic gonadotropin (hCG) from early pregnancy stimulates the thyroid gland to an increased production of thyroid hormone. hCG is a glycoprotein synthesized in and released from the placenta, and it stimulates the TSH receptor due to structural similarities with TSH.[9] Gestational hyperthyroidism is a nonautoimmune transient disorder that occurs in the first trimester of pregnancy and is caused by the peak in hCG levels during early pregnancy.[4,5] Gestational hyperthyroidism is often associated with hyperemesis gravidarum, and clinically it may be difficult to distinguish from Graves' hyperthyroidism. The presence of TRAb strongly supports a diagnosis of Graves' disease.[2–4]

Graves' disease.[2–4]

The incidence of Graves' disease varies in and around pregnancy.[10] Pregnancy is associated with profound changes in the maternal immune system, with a general immune suppression during the pregnancy followed by an immune rebound after the birth of the child.[11]

The women identified with hyperthyroidism in early pregnancy did not suffer from transient hyperthyroidism,[10] but it can be speculated that the hCG-medicated increase in thyroid hormone production in early pregnancy may trigger the development of Graves' disease in susceptible individuals.[12] Likewise, Graves' disease that developed prior to a pregnancy may aggravate in early pregnancy.[13]

Diagnosis of hyperthyroidism in pregnancy
Changes in thyroid hormone metabolism

The diagnosis of overt hyperthyroidism is based on the measurement of a suppressed TSH and an elevated T3 and/or T4.[1–3] The physiological changes during a pregnancy may, however, challenge the interpretation of thyroid function test results.[9] One physiological mechanism is the increase of hCG in early pregnancy that stimulates the thyroid gland to increase production of thyroid hormone and tends to decrease TSH.[9] Another physiological mechanism is the increased activity of the type-3-deiodinase enzyme in the placenta that

inactivates T3 and T4 and tends to increase TSH.[9] Finally, the pregnancy-associated high levels of estrogen increase thyroxine-binding globulin with a concomitant increase in total T3 and total T4.[9]
One consideration related to these physiological changes is how to evaluate the peripheral thyroid hormone concentrations in pregnant women. The change in thyroxine-binding globulin concentrations, and thereby in the concentration of totalthyroid hormone, has led to the use of free thyroid hormone assays in many countries. Direct measurement of free thyroid hormone concentrations includes an initial separation of free and protein-bound thyroid hormone by ultrafiltration or equilibrium dialysis. However, in routine laboratories, free thyroid hormones are usually determined using automatic immunoassays, and all these provide an indirect measurement of free thyroid hormone concentrations with no initial separation. Thus, free thyroid hormone concentrations change in relation to the physiological changes during a pregnancy.[14] Furthermore, the methods used to determine the free thyroid hormone concentrations in different immunoassays are not identical, and this diversity stresses the importance of laboratory-specific reference ranges.[15]

Untreated hyperthyroidism in pregnancy
Fetal programming
Correct diagnosis of hyperthyroidism in pregnant women is important to prevent adverse outcomes of pregnancy. Overt hyperthyroidism is considered as a clinical high-risk situation, and the disease should be carefully diagnosed, managed, and controlled.[2–4] On the other hand, subclinical hyperthyroidism (suppressed TSH) has not been associated with pregnancy complications.[17]

Thyroid hormones are important developmental factors.[18] Thyroid hormone receptors are present in the maternal–fetal unit,[19] and normal levels of thyroid hormone are important in the maintenance of a normal pregnancy.[20] Both the lack of thyroid hormone and thyroid hormone excess may interfere with the maternal–fetal unit, and women suffering from hyperthyroidism have an increased risk of both early and late pregnancy loss.[21] Maternal hyperthyroidism is also associated with an increased risk of preterm delivery and low birth weight of the child and may seriously complicate the health of the pregnant women, eg, maternal heart failure and in rare cases even thyroid storm

Symptoms of Hyperthyroidism
Common in pregnancy –
Heat intolerance
Diaphoresis
fatigue
anxiety
emotional lability
tachycardia
wide pulse pressure
nausea/vomiting
Abnormal presentations
Weight loss
Pulse>100bpm
Diffuse goiter
Tremor
Systolic HTN
Diarrhea

Clinical recommendations-
Ask about symptoms
If suspicious

Check TSH and free T4 (caution if 8-12 weeks)
–Thyroid exam àultrasound if nodule/goiter

Diagnosis
GREATLY suppressed TSH
–TSH undetectable in 10-20% of NORMAL
If TSH <0.1 mU/mL àcheck free T4
–If elevated: hyperthyroid!
–If free T4 normal, check free T3

Treatment
Always best to optimize prior to conception

Risk of uncontrolled hyperthyroidism far outweighs risk of therapy
Can consider no treatment if very minimal elevation of T4/T3Treatment
Goal of therapy is control WITHOUT causing fetal or neonatal hypothyroidism

Keep free T4 in HIGH-normal range or total T4 at 1.5x upper limit of normal

Medications
Thioamides: propylthiouricil(PTU) and methimazole(MMI)
–inhibit synthesis of thyroid hormones
–PTU also inhibits peripheral conversion of T4 T3

PTU vsMMI
Both cross the placenta with equal kinetics
Several reports of aplasia cutis with MMI
–0.03% = baseline risk

Reports of choanalatresia, omphalocele, tracheoesophagealfistula PTU associated with reports of severe, fatal liver failure Current ThioamideRecommendations
Limit PTU use to first trimester only
Switch from PTU to MMI at 13-14 weeks
–MMI 20-30x as potent as PTU per mg
300mg PTU=10-15mg MMI

Monitor **free T4** every 4 weeks
–When stably high normal, q trimester

In reality, most have MMI(methamazole) through entire pregnancyThionamideDosing
Methimazole(MMI)
Start with 5-10 mg BID
Increase to 10-40 mg daily

Propylthyouricil(PTU)
Start with 50mg BID/TID
Increase to 100mg TID
Max 150mg TID in severe cases

300mg PTU=10-15mg MMI

Monitor **free T4** every 4 weeks
–When stably high normal, q trimester
In reality, most have MMI through entire pregnancy
ThioamideSide effects
Agranulocytosisin 0.2-0.5%
–Check baseline CBC
–Counsel about risk
Acute liver failure
Rash, arthralgias
Other Therapies
Beta blockers (propranolol)
Iodides
Radioactive ablation and surgery (contraindicated)
Subclinical Hyperthyroidism
Low TSHwith normal free T4/T3
No increased risk of pregnancy complications
No need to follow or treat

Gestational Transient Thyrotoxicosis
1-3% of pregnancies
hCGstimulation of the thyroid leads to elevated free T4
Peaks between 8-14 weeks
No thyromegaly
Not associated with adverse pregnancy outcomes
Fetal and Neonatal Hyperthyroidism
Typically due to TSIs crossing placenta
Occurs in 1% of Grave's pregnancies
Remember: TSIs persist after surgery or radioactive iodine ablation
Some measure TSIs in pregnancy
–We argue not to

Fetal Thyrotoxicosis
Heart rate >160 bpm
Growth retardation
Advanced bone age
Goiter
Craniosynostosis
Newborn Thyrotoxicosis

Important: notify pediatrician
Evaluate at birth and after 48 hours
Thyroid Storm
2% of women undergoing treatment for hyperthyroidism
Biggest risk factor is no treatment or incomplete treatment
Thyroid Storm Presentation

CNS effects (agitation, delirium, coma)
Thermoregulatory dysfunction (fever)
GI dysfunction
Cardiovascular problems (tachycardia, heart failure)

Thyroid Storm Precipitants
Labor
Delivery
Cesarean
Infection
Preeclampsia
Thyroid Storm Treatment
PTU: 600mg orally/crushed via NG tube
Iodide (start 1 hour after PTU): 2-5 drops SSKI q8 hr
Dexamethasone: 2mg q6hrs x4 doses
–To block T4àT3 conversion
Propranolol: 12mg IV q5 min for severe tachycardia plus 20-80mg PO/NG q6hr
Summary for Hyperthyroidism/Grave's

PTU in first trimester/MMI after first trimester
Ultrasound at 18-22 weeks for anatomy
Growth ultrasound at 32 weeks
Weekly NSTs at 34 weeks (optional)
Notify pediatrician
Postpartum follow up

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