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Pregnancy and maternal hyperthyroidism: A review

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Abstract
Thyroid disease is the second most common endocrine disorder associated with pregnancy. Graves disease accounts for most of the cases of pregnancy-associated hyperthyroidism. It is associated with an increased incidence of maternal and perinatal complications. Pre-conceptional achievement of euthyroid state is advised. Serum thyroid profile is diagnostic.The mainstay of management is anti-thyroid drugs. Other available options are beta-adrenergic blockers and sub-total thyroidectomy. Thyroid storm is an obstetric emergency and is to be managed in obstetric intensive care unit. Early diagnosis and management of maternal hyperthyroidism plays the key role in improving pregnancy outcomes.

Keywords: Hyperthyroidism, Maternal, Pregnancy, Thyrotoxicosis

Introduction
A variety of endocrine disorders can complicate pregnancy and vice-versa. Thyroid disease is the second most common endocrine condition affecting women of reproductive age[1]. It is now common for obstetricians to care for women who enter pregnancy with an established thyroid deficiency or overactive state. Hyperthyroidism complicates approximately 1-2 in 1000 pregnancies.[1,2,3,4] The overwhelming cause of hyperthyroidism during pregnancy is Graves disease or autoimmune thyrotoxicosis[1,2,3,4], an organ-specific auto-immune process usually associated with thyroid stimulating antibodies. This article reviews hyperthyroidism in relation to pregnancy, with an aim to reduce the fetal and maternal morbidity and mortality associated with the condition.

Causes
Graves disease accounts for more than 90% of these cases.[1,2,3,4] The other causes of hyperthyroidism during pregnancy include toxic multi-nodular goiter (rare in reproductive age group), toxic adenoma, thyroiditis (chronic, sub-acute, viral) and exogenous thyroid hormone administration[1]. Hyperthyroidism may also result from elevated serum levels of hCG, as seen with trophoblastic diseases and hyperemesis gravidarum[1].

Diagnosis
Normal pregnancy simulates some clinical findings similar to thyroxine excess, so mild thyrotoxicosis may be difficult to

diagnose.[3,4] Suggestive findings include nervousness, heat intolerance, palpitations, goiter or thyromegaly, failure to gain weight or weight loss, hyperemesis gravidarum, fatigue, increased appetite, increased urinary frequency, insomnia and emotional lability.[1,2,3,4] More specific symptoms and signs include tremor, nervousness, frequent stools, excessive sweating, brisk reflexes, muscle weakness, goiter, hypertension and weight loss[1]. Graves ophthalmopathy (stare, lid lag and retraction, exophthalmos) and dermopathy (localized or pretibial myxedema) are diagnostic[1]. Tachycardia exceeding that usually seen with normal pregnancy is suggestive.[3,4]

Laboratory diagnosis of hyperthyroidism is confirmed with a suppressed serum thyrotropin (TSH) along with an elevated serum free T_4 (fT_4) level[1,3]. Rarely hyperthyroidism is also caused by abnormally high serum triiodothyronine values (T_3 thyrotoxicosis)[3].

Subclinical hyperthyroidism is defined as serum TSH concentration below the statistically defined lower limit of normal with a serum concentration of fT_4 within the reference range[2]. Evaluation of fT_3 or free T_3 index may also be useful in such patients[2].

Also, evaluation of TSH-receptor antibodies may be helpful in women with Graves disease to identify those at risk for delivery of an infant with fetal or neonatal hyperthyroidism[2].

Pre-conceptional counselling

The optimal time to conceive is once a euthyroid state is achieved[5]. Pre-pregnancy counseling of all patients with hyperthyroidism or a history of hyperthyroidism is imperative and use of contraception until the disease is controlled is strongly recommended[5]. Prior to conception, a hyperthyroid patient may be offered ablative therapy (I^{131} or surgery) or medical therapy[5]. Radioactive iodine administration is contraindicated during pregnancy because of the risk of fetal thyroid ablation.[1,3,6] It is recommended that women avoid pregnancy or breast-feeding for 4-6 months after I^{131} therapy.[1,3,6] Inadvertent use of I^{131} in early pregnancy, up to 10 weeks is usually not associated with long term fetal or neonatal thyroid side-effects.[1,6] However, this agent may cause permanent damage to the fetal thyroid if used after 10-12 weeks of gestation.[1] Thus, when given unintentionally, most clinicians recommend abortion.[3] Any exposed infant must be carefully evaluated for hypothyroidism.[3]

Pregnancy outcome

Pregnancy outcomes largely depend on whether metabolic control is achieved.[3] Untreated hyperthyroidism poses considerable maternal and fetal risks including IUGR, preterm delivery, severe preeclampsia and heart failure.[1,3] The disease usually worsens in the first trimester and moderates later in pregnancy.[1]

Fetal and neonatal implications

Perinatal risks include IUGR, prematurity, non-immune hydrops, cardiac dysrhythmias and intrauterine demise.[1,3] Clinical hyperthyroidism occurs in approximately 1% of neonates born to mothers with Graves disease.[7] Neonates of women with thyrotoxicosis are at risk for immune mediated hypothyroidism as well as hyperthyroidism secondary to auto-antibodies that may cross the placenta (Graves disease and chronic autoimmune thyroiditis).[1] Maternal auto-antibodies are cleared slowly in the neonate sometimes resulting in delayed presentation of neonatal Graves disease.[1]

Fetal Diagnosis

Ultrasonography of the fetal thyroid gland, performed by an experienced person, is an excellent diagnostic tool in suspected cases[7]; however, most investigators do not currently recommend routine evaluation[3]. Percutaneous fetal blood sampling has also

been proposed in selected cases like those with associated hydrops, growth restriction, goiter or tachycardia[8].

Maternal complications

Maternal risks associated with untreated hyperthyroidism include preeclampsia, heart failure, infection, anemia and thyroid storm.[1,2,3]

Thyroid Storm: is a rare but potentially fatal complication of hyperthyroidism, characterized by cardiovascular compromise (tachycardia out of proportion to the fever, dysrhythmia, cardiac failure), hyperpyrexia and central nervous system changes (restlessness, nervousness, changed mental status, confusion and seizures).[1] The pregnant woman with thyrotoxicosis has minimal cardiac reserve and decompensation is usually precipitated by preeclampsia, anemia, sepsis or a combination of these.[3,6] Other precipitants of thyroid storm include acute surgical emergency, induction of anesthesia, labor and delivery, noncompliance with anti-thyroid medications, diabetic keto-acidosis, myocardial infarction and pulmonary embolism.[1] Diagnosis can be difficult and if delayed, the patient may lapse into shock and/or coma.[1] Laboratory profile reveals leucocytosis, elevated liver enzymes, and occasionally hypercalcemia.[1] Thyroid function test results are consistent with hyperthyroidism but do not always correlate with the severity of the thyroid storm.[1]

Management

Management of hyperthyroidism with pregnancy requires special considerations because pregnancy induces major changes in thyroid function and maternal thyroid disease can have adverse effects on the pregnancy and fetus.[9] The primary objective of treatment is to effectively control thyroid function until after delivery.[1] Protecting the fetus from the effects of disease and the side effects of the medical regimen is a secondary yet important objective.[1] Avoiding maternal (and fetal) hypothyroidism is of major importance because of potential damage to fetal neurological development and an increased incidence of miscarriage and preterm delivery.[9] Care requires coordination between several health care professionals.[9]

Observation alone may be a reasonable treatment plan for mild clinical disease.[1,2] Overt thyrotoxicosis during pregnancy can nearly always be controlled by thioamide drugs and treatment has been associated with improved pregnancy outcomes.[2]

Anti-thyroid drugs

Anti-thyroid drugs are the mainstay of treatment of hyperthyroidism during pregnancy.[1] Anti-thyroid medications available include propylthiouracil (PTU), methimazole (MMI) and carbimazole.[1]Since carbimazole is rapidly metabolized to methimazole, these two drugs are essentially the same.[1]

Propythiouracil (PTU) or 6-n-Propylthiouracil is a thioamide drug used to treat hyperthyroidism by decreasing the amount of thyroid hormone produced by the thyroid glands.[10] PTU inhibits the enzyme thyroperoxidase, which normally acts in thyroid hormone synthesis by oxidizing the anion iodide (I^-) to iodine (I^0), facilitating iodine's addition to tyrosine residues on the hormone precursor, thyroglobulin.[10] It also acts peripherally by inhibiting the enzyme 5'-deiodinase, which converts T_4 to the active form T_3.[10] (This is in contrast to MMI, which shares PTU's central mechanism, but not its peripheral one.[10]

The greatest concern with the use of anti-thyroid drugs in pregnancy is related to teratogenic effects.[5] PTU was US FDA approved in 1947 but PTU is classified as Drug Class D in pregnancy, signifying that there is positive evidence of human fetal risk.[10] Maternal benefit may outweigh risk in life-threatening situations.[10] Exposure to MMI may produce several congenital malformations, mainly aplasia cutis and the

syndrome of "MMI embryopathy" that includes choanal or esophageal atresia and dysmorphic facies.[5,11] Although very rare complications, they have not been reported with the use of PTU.[5] Besides this, PTU also partially inhibits the conversion of T_4 to T_3 and crosses placenta less readily than MMI.[11] So, PTU is preferred over MMI (which is also a Class D Drug) by some clinicians.[3] Recently, a report from the Adverse Event Reporting System of the US FDA called attention to the risk of hepatotoxicity in patients exposed to PTU; an advisory committee recommended limiting the use of PTU to the first trimester of pregnancy, patients with MMI allergy and in management of thyroid storm.[5] In the second and third trimester, MMI is preferred.[5]

Dosage

Equivalent doses of PTU to MMI are 10:1 to 15:1 (100 mg of PTU = 7.5 to 10 mg of MMI) and those of carbimazole to MMI are 10:8.[5] The initial dosage depends on the severity of hyperthyroidism.[5] In general, the initial doses are: MMI 5-15 mg daily; carbimazole 10-15 mg daily and PTU 50-300 mg daily in divided doses.[3,5] Lack of response is usually due to non-compliance and may require hospitalization.[5] Most women (90%) will have improvement within 2 to 4 weeks.[5] Rapid improvement necessitates a decrease in dosage.[5] The goal of treatment is to use the smallest dose that maintains maternal free T_4 levels at or just above the upper limit of normal.[1,5,6]

Monitoring

Clinical and laboratory follow- up (TSH, free T_4, free T_3) should be done every 2 to 4 weeks.[1] Serum free T_4 is considered a better indicator of thyroid status than TSH during the first 2-3 months of treatment for hyperthyroidism.[12] Baseline white blood cell (WBC) and liver function test should be obtained before initiating anti-thyroid therapy, since hyperthyroidism itself as well as anti-thyroid drugs may cause liver enzyme elevations and leucopenia.[1,3] Monitoring blood counts and liver function is advised.[1]

Side effects

Side effects occur in 3-5%,[10] mostly allergic and skin reactions such as rash, itching, hives, abnormal hair loss and skin pigmentation.[5,10] Other minor side effects include nausea, anorexia, fever, arthralgias and loss of taste or smell.[1] The greatest concern however, is related to teratogenic effects, leucopenia and hepatotoxicity. Transient leucopenia can be documented in up to 10% and the incidence of agranulocytosis with thioamides is about 0.1-0.4%.[1,3] This is usually heralded by fever and sore throat and these symptoms should precipitate immediate discontinuation of the drug and checking for leucopenia.[1,3,6] Owing to the risk of hepatotoxicity, especially with PTU, liver function should be monitored and anti-thyroid medication should be discontinued if liver function values become alarming.[1] Other major but rare side effects include a lupus like syndrome, thrombocytopenia and hepatitis/hepatic infarction.[1] About 20% of the patients may develop antineutrophil cytoplasmic antibodies (ANCA) but only a few develop serious vasculitis.[1,3]

Beta-adrenergic blockers

Beta adrenergic blocking agents, such as propranolol 20-40 mg every 6-8 hours, may be used for controlling hyper-metabolic symptoms, tremor and palpitations, until the thioamides decrease thyroid hormone levels.[1,5] The dose should be reduced as clinically indicated, usually within 2-6 weeks.[5] Long-term treatment with beta-blockers has been associated with intra-uterine growth restriction, fetal bradycardia and neonatal hypoglycemia.[1,5] Beta-blockers may also be used as preparation for thyroidectomy and in the management of thyroid storm.[5] Relative contra-indications

to the use of beta-adrenergic blockers include obstructive lung disease, heart block, heart failure and insulin use.[1]

Subtotal thyroidectomy

Indications for thyroidectomy include:[1,3,5,6]

- Allergies/contraindications to both anti-thyroid drugs.
- Severe anti-thyroid drug side-effects.
- Women requiring large doses of anti-thyroid drugs or failed medical suppression of thyroid function.
- Noncompliance with drug therapy.

To minimize pregnancy complications, surgery is usually performed during the second trimester.[1] Preoperatively, hyperthyroidism should be controlled with anti-thyroid medication for 7-10 days, a beta-adrenergic blocker (propranolol, 20-40 mg, 3-4 times daily) and inorganic iodide (Lugol's solution, 3 drops, twice daily) for 4-5 days.[1,3]

Thyroid storm

The gold standard of treatment of thyroid storm is primary prevention.[13] Prevention of thyroid storm requires careful control and management of hyperthyroidism.[13] Treatment should, however, be initiated on suspicion of the condition and the clinician should not wait for laboratory confirmation before starting therapy.[1] Thyroid storm requires prompt recognition, aggressive reversal of thyroid dysfunction and supportive management of signs and symptoms. Management is best accomplished in an obstetric intensive care unit.[13]

The basic goals of therapy are to[1] :

- Reduce the synthesis and release of thyroid hormone.
- Remove thyroid hormone from the circulation and increase the concentration of thyroid-binding globulin.
- Block the peripheral conversion of T_4 to T_3.
- Block the peripheral actions of thyroid hormone.
- Treat the complications of thyroid storm and provide support.
- Identify and treat the potential precipitating conditions.

To these ends, a standard series of drugs are used:

I. Propylthiouracil or methimazole, both of which inhibit iodination of tyrosine leading to reduced synthesis of thyroid hormones. PTU also blocks peripheral conversion of T_4 to T_3. PTU is commonly used by oral or nasogastric route, as 300-1000mg loading dose followed by 150-200 mg orally every 4-6 hours.[1,3,6]

II. Iodide is initiated 1-2 hours after PTU, in order to inhibit thyroidal release of T_3 and T_4, by inhibiting the proteolysis of thyroglobulin. Iodides can initially increase the level of thyroid hormones so it is essential to start PTU prior to giving iodides. Following forms of iodides can be used: a) Oral supersaturated solution of potassium iodide, 2-5 drops orally every 8 hours. b) Intravenous sodium iodide, 500-1000mg every 8 hours. c) Oral Lugol's iodine solution, 8-10drops every 6-8 hours.[1,3,6]

III. With a history of iodine-induced anaphylaxis, oral lithium carbonate, 300mg every 6 hours has been used. (therapeutic level = 1meq/L)[1,3,6]

IV. Adrenal glucocorticoids should be started as soon as the condition is diagnosed. They block the release of stored hormones as do iodides and block peripheral conversion of T_4 to T_3 as do the thioamides. Dexamethasone is given as 2mg intravenous or intramuscular, every 6 hours for 4 doses. Hydrocortisone 300mg per day intravenous or prednisolone 60mg per day can also be used.[1,3,6]

V. Beta adrenergic blockers effectively control tachycardia and hyper-metabolic symptoms. Propranolol, labetalol and

esmolol have all been used intrapartum. If a beta-blocker is used to control tachycardia, its effect on heart failure must be considered.[14] Propranolol, 20-80mg orally or by nasogastric tube every 4-6 hours is used. It is also given 1-2mg/minute intravenous for 5 minutes for a total of 6mg followed by 1-10mg intravenous every 4 hours.[1]

VI. If the patient has history of severe broncospasm, reserpine, guanethidine or diltiazem may be used.[1,6]

VII. If sedation is required, phenobarbitone may be used to control restlessness. 30-60mg orally every 6-8 hours may be given.[1,6]

VIII. Co-existing severe preeclampsia, infection or anemia should be aggressively managed.[3]

IX. General supportive measures, such as oxygen, antipyretics and appropriate monitoring are also important. The perceived underlying cause of thyroid storm should be treated.[6]

X. Plasmapheresis or peritoneal dialysis to remove circulating thyroid hormone is an extreme measure reserved for patients who do not respond to conventional therapy.[1]

Depending on the gestational age, fetal status should be evaluated with ultrasound examination, non-stress testing or a biophysical profile. Unless deemed necessary, delivery during thyroid storm should be avoided.[6]

Conflict of interest

None

Conclusion

Early diagnosis and appropriate management of maternal hyperthyroidism can help reduce maternal and perinatal morbidity and mortality resulting in improved pregnancy outcomes. Universal screening of women for thyroid disease is not yet supported by adequate studies but case finding targeted to specific groups who are at increased risk is strongly supported.

References

1. Belfort MA. Thyroid and Other Endocrine Emergencies. Foley MR, Strong TH Jr., Garite TJ. Obstetric Intensive Care Manual 3rd Ed. New Delhi. Tata McGraw-Hill. 2011:117-23.
2. Casey B. Maternal hypothyroidism and hyperthyroidism. Queenan JT, Spong CY, Lockwood CJ. Management of High-Risk Pregnancy 5th Ed. Blackwell Publishing 2009:188-91.
3. Cunningham, Leveno, Bloom et al. Thyroid and other Endocrine Disorders. Williams Obstetrics 23rd Ed. Mc Graw-Hill 2010:1126-30.
4. Thyroid Problems. www.emedicinehealth.com >…> thyroid and metabolism a-z list
5. Stagnaro-Green A, Abalovich M, Alexander E et al. Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and Postpartum. Thyroid 2011; 21:1081.
6. Schroeder BM. ACOG Practice Bulletin on Thyroid Disease in Pregnancy. Am Fam Physician 2002 May 13; 65(10):2158-62.
7. Luton D, Le Gac I, Vuillard E, et al. Management of Grave's disease during pregnancy: The key role of fetal thyroid gland monitoring. J Clin Endocrinol Metab 2006; 90: 6093-98.
8. Brand F, Liegeois P, Langer B. One case of fetal and neonatal variable thyroid dysfunction in the context of Graves disease. Fetal Diag Ther 2005.20(1):12-5.
9. Abalovich M, Amino N, Barbour LA, et al. Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metabol 2007 Aug; 92(8): s1-7.
10. Propylthiouracil – Wikipedia. en.wikipedia.org/wiki/Propylthiouracil

11. Diav-Citron O, Ornoy A. Teratogen Update: antithyroid drugs – methimazole, carbimazole and propylthiouracil. Teratology 2002 Jan; 65(1): 38-44. (onlinelibrary.wiley.com/doi/10.1002/tera.1096/abstract)
12. National Academy of Clinical Biochemistry: NCAB, Laboratory Support for the diagnosis and monitoring of thyroid disease. Washington. National Academy of Clinical Biochemistry 2002, p125.
13. Patricia AW, Joyce MB, Sharon L. Thyroid Storm During Pregnancy: A Medical Emergency. Critical Care Nurse 2004; 24: 74-79.
14. Bowman ML, Bergmann M, Smith JF. Intrapartum labetalol for the treatment of maternal and fetal thyrotoxicosis. Thyroid 1998 Sep; 8(9): 795-6.