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Review Article

MANAGEMENT OF HYPERTHYROIDISM IN A PREGNANT WOMAN (REVIEW)

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A B S T R A C T

Thyroid disorders are common in pregnancy and can result in serious complications for the pregnant women and her child. During pregnancy hyperthyroidism is uncommon an occur in<1% of cases Hyperthyroidism in a women who are of childbearing age is predominantly of auto immune in origin caused by Graves disease. 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 foetus, particularly the foetal brain. Early identification and adequate management of hyperthyroidism in a pregnant woman is essential, because uncontrolled thyrotoxicosis significantly increases the risk of maternal and foetal complication. The treatment of choice in pregnancy is Antithyroid drugs (ATDs). Birth defects have been reported in association with the use of ATDs during early pregnancy. Because of the above consideration the management of pregnant women with hyperthyroidism requires special care bearing in mind that both maternal thyroid excess perse and related treatment may adversely affect the new born health. In this reviews we discuss the diagnosis and management of hyperthyroidism in pregnancy along with the impact of hyperthyroidism on pregnancy and synthesis the treatment options during pregnancy and lactation.

INTRODUCTION

Thyroid disorders are common in a woman of reproductive age. Hyperthyroidism is a relatively uncommon condition in pregnancy, with a new diagnosis in about 0.05% of all pregnant women.[1] .In addition as hyperthyroidism is common in women of reproductive age, many women with previously diagnosed hyperthyroidism become pregnant. The two most common causes of hyperthyroidism in pregnancy are (a)gestational transient thyrotoxicosis and (b)Graves disease. Toxic multinodular goiter, toxic thyroid nodule, thyroiditis and drugs are rare causes of thyrotoxicosis in pregnancy, while trophoblastic disorders(hydatidiform mole and choriocarcinoma), Struma ovarii, non autoimmune hyperthyroidism due to activating TSH receptor mutation and TSH secreting pituitary adenoma are extremely rare.[1].

Hyperthyroidism in pregnancy is a special clinical situation because physiological changes related to the pregnant state challenge the interpretation of thyroid function test. Identification of hyperthyroidism in a pregnant woman is essential because unfavorable outcomes can occur in both the mother and the foetus. Hyperthyroidism can be overt and subclinical.. In general, subclinical hyperthyroidism rarely associated with adverse gestational outcomes [2], whereas uncontrolled thyrotoxicosis significantly increases the risk of maternal and fetal complications. Besides the severity of maternal hyperthyroidism, additional factors that may affect fetal prognosis include the transplacental passage of maternal TSH receptor antibodies (TRAb) or thyrostatic agents, both of which may disrupt fetal thyroid function. Antithyroid drugs has been linked to increases the risk of birth defect and maternal liver injury. In this review we discuss the diagnosis and management of hyperthyroidism in pregnancy along with the impact of hyperthyroidism and ATD on foetal outcome.

Changes in Maternal Thyroid Physiology in Pregnancy

A normal pregnancy results in a number of important physiological and hormonal changes that alter thyroid function. These changes mean that laboratory test of thyroid function must be interpreted with caution during pregnancy. Thyroid function tests changes during pregnancy due to the influence of two main hormones, HCG and Estrogen. [3]

HCG which similar to TSH stimulates the thyroid gland and increase the level of thyroxin hormone .The resultant effect is a significant decline in TSH concentration during first

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trimester reaching a nadier around 10 weeks gestation when the HCG level is at its peak. Estrogen significantly increases the amount of serum thyroxin binding globulin (TBG) from the first trimester and remains high until term. The increase in TBG concentration is responsible for an increase in total T4 and T3 concentration and is accompanied by a contextual decrease in free thyroid hormone level (10-15%). This decrease is partially offset by an increase in thyroid hormone output by a normally functioning thyroid gland.

Because of the above changes TSH level found below or near the lower limit of the reference range during the first trimester of pregnancy may not be indicative of maternal hyperthyroidism as they are found in as many as 15% of healthy pregnant women at this stage pf pregnancy ,further biochemical investigations and accurate clinical evaluation should be performed to confirm hyperthyroidism.

Assessment of thyroid function in pregnancy

The dynamic physiological changes involving the thyroid axis at different stages of pregnancy impacts on the assessment of thyroid function in pregnant women in several ways.

- Firstly the reference ranges of thyroid function test for pregnant women are different from those of non pregnant general population.
- Secondary the thyroid stimulating action of HCG and the varying level of circulating HCG in different trimesters means trimester-specific ranges of TSH and free thyroid hormones are necessary to assess thyroid function in pregnancy.
- Thirdly the measurement of free thyroid hormones(freeT4and freeT4) when carried out using an automated immunoassay is affected by changes in TBG and albumin levels in pregnancy leading to a substantial decrease in free T4 levels in the third trimester. However, this problem is assay dependant, with the effect more pronounced with some assays than the other. The establishment and the use of assay specific reference ranges can ameliorate the problem to some extent
- Finally because of the above- mentioned problems associated with measurement of free thyroid hormones, some expert recommend the use of total thyroid hormones (Total T4 and Total T3) levels in pregnancy. However, because of increase in TBG level during pregnancy, total thyroid hormone levels are higher than in non pregnant state. If total T4 is measured in pregnancy, the reference range should be adjusted depending upon the gestation age at the time of test(gestational age:<7 weeks-no adjustment ,7-16 weeks-increase upper limit of the non pregnant reference range by 5% per week starting at week 7, >16weeks - 50% higher than the prepregnancy reference range) .[4] Total thyroid hormone assays are no longer in routine use in many countries.

Reference TSH values (mlU/L) According to different societies in Pregnancy

YEAR	First trimester	Second trimester	Third trimester
ITS 2012	<2.5	<3.0	<3.0
ETA 2014	<2.5	<3.0	<3.0
ATA 2017	Use locally derived reference ranges from a specified pregnant population. If above is not available use 0.5-4.0 mlU/L.		

ATA: American Thyroid Association; ETA:European Thyroid Association ,ITS: Indian Thyroid Society [4]

Etiology of Hyperthyroidism in Pregnancy

The two most common cause of thyrotoxicosis in pregnancy are:(a)gestationa transient thyrotoxicosis and (b)Graves disease[1]

Gestational transient thyrotoxicosis[GTT)

This is the most common cause of hyperthyroidism during pregnancy, and may occur in 1---3% of all pregnancies. It has been defined as a transient hyperthyroidism which is limited to the first half of pregnancy and characterized by increased FT4 or TT4 (adjusted) levels with suppressed or undetectable TSH in the absence of thyroid auto antibodies or physical features suggesting Graves' Disease.[5] This is usually the result of increased HCG levels or from a greater affinity for TSH receptors. The most characteristic condition within this group is *hyper emesis gravidarum* (HG), but there are other conditions also associated with increased HCG levels such as multiple pregnancy or trophoblastic disease (hydatid mole or choriocarcinoma) with a GTT prevalence up to 50%. There are also other less common causes such as *hyperreactio luteinalis*, characterized by the formation of theca-lutein cysts in the setting of pregnancy, or hyperplacentosis, where increased placental weight and HCG production are seen. There is also a familial condition (familial gestational thyrotoxicosis) where hypersensitivity of the TSH receptor to physiological HCG levels occurs due to a dominant autosomal mutation, this is clinically characterized by GTT development in all pregnancies and all women in the family with normal HCG levels.[6]

Hyperemesis gravidarum[HG]

The most common cause of GTT is HG. HG occurs in 0.5---10/1000 of all pregnancies, and is associated with increased free Thyroid hormone levels and TSH suppression in 30---60% of cases. It should be noted that the concept of HG should be restricted to conditions associated in the first trimester of pregnancy with vomiting, dehydration, loss of at least 5% of body weight, and ketonuria.[7] In these cases, hyperthyroidism is characterized by the suppression of TSH levels and minimum FreeT4 increases, with commonly normal FreeT3 levels. Thyroid hyper function, as well as associated vomiting, usually resolve spontaneously before week 20, and symptomatic treatment with intravenous hydration and vitamin B complex is sufficient to prevent the exceptional risk of Wernicke's encephalopathy. There is no evidence that treatment with anti-thyroid drugs (ATD) provides any benefit, and their use is therefore inadvisable.[8] Exceptionally, HG with a highly conspicuous thyroid hyper function component or GD with associated gastrointestinal intolerance (nausea and vomiting) may suggest the need for differential diagnosis between them.

Table 1 Differences between Graves' disease and hyper emesis Gravidarum

Sign	Graves' disease	Hyperemesis Gravidarun
Symptoms of thyrotoxicosis	Present	Often absent and mild
Goitre	Often present	Absent
Thyroid eye disease	May be present	Absent
TSH receptor antibodies	Present	Absent
Resolution of thyrotoxicosis	Tends to improve in later pregnancy	Remit in the second half of pregnancy
Adverse obstetric outcomes	Associated in case of suboptimal control of thyrotoxicosis	No association

Table- 1 shows the main differences. In any case, if hyperthyroidism lasts beyond the first trimester of pregnancy, a cause other than GTT should be suspected. Although biochemical evidence of hyperthyroidism is usually associated with serum HCG levels of 100,000–500,000 IU/L, the diagnostic usefulness of serum HCG measurement is limited, unless gestational trophoblastic diseases are suspected [9]. Analogously, thyroid ultrasonography is usually poorly informative, and it is mostly performed to distinguish GTT from GD. Likely because of its short and self-limiting course, GTT is not associated with significant obstetrical complications and adverse neonatal outcomes. However, children born to mothers experiencing GTT complicated by severe hyper emesis and weight loss of > 5% of their prepregnancy weight have been reported to have significantly lower birth weight as compared to gestational-age matched infants born to unaffected mothers [5].

Concerning treatment, in most cases GTT does not require any treatment because of its spontaneous recovery within a few weeks. Anti thyroid drugs are not indicated, since thyrotoxicosis usually recovers by 14–18 weeks of gestation. When GTT is associated with severe hyper emesis (> 5% weight loss, dehydration, and ketonuria), in addition to treatment with fluids and electrolytes, propranolol may be transiently given, because of its efficacy in reducing hyperemesis and symptoms of thyrotoxicosis [4].

Graves' disease (GD) in pregnancy

Graves disease is the most common cause of hyperthyroidism in women of childbearing age, occurring before pregnancy in 0.4–1.0% women and in approximately 0.2% pregnant women [1]. The pathogenesis of hyperthyroidism due to GD in a pregnant woman is the same as in non pregnant patients, as it results from thyroid overstimulation by Thyroid receptor antibodies (TRAbs). As for other autoimmune diseases, Graves disease typically improves during the 2nd and 3rd trimesters, and often relapses in the post-partum period. This evolution mostly reflects the pattern of changes in TRAb levels occurring during gestation, as a result of the tolerogenic state that takes place during normal pregnancy [10]. Gestational immune tolerance, ultimately aimed at avoiding the fetus to be rejected as foreign tissue while maintaining the mother and fetus protected against infections, involves a complex interplay between hormonal factors, immunological molecules of trophobastic origin and specific T-cell subsets, regulatory T cells [TREG] generated within the maternal decidua. Besides maintaining fetal alloantigen tolerance, TREG cells migrating to the maternal circulation indirectly induce a state of generalized and transient immune-suppression, which explains either the observed amelioration of GD during pregnancy or the rare de novo gestational onset of GD [11-13]. However, although clinical and biochemical features of thyrotoxicosis usually improve with the progression of pregnancy, a transient worsening of hyperthyroidism during the 1st trimester due to the thyroid-stimulating activity of HCG is not infrequently observed . Finally, following delivery, the abrupt fall of TREG cells provides an explanation for the rebound of post-partum thyroid autoimmunity, with either worsening or re-exacerbation of GD [13].

Diagnosis of Graves Disease in Pregnancy

From a diagnostic point of view, women with a history of Graves disease already known prior to conception obviously pose no problems. In contrast, diagnosis of Graves disease first occurring during pregnancy may be difficult, because many clinical symptoms of hyperthyroidism such as palpitations, sleeplessness, anxiety, fatigue, are nonspecific and may be overlooked or interpreted as normal pregnancy symptoms. However, symptoms and signs like failure to gain weight or weight loss despite an increased food intake, presence of goiter, or ocular changes are highly suggestive of a diagnosis of hyperthyroidism due to GD in a pregnant patient [4]. Clinical diagnosis of hyperthyroidism is made based on biochemical thyrotoxicosis (elevated serum free T4 or freeT3 with suppressed serum TSH) If biochemical hyperthyroidism is detected, measurement of TRAbs is indicated, since the presence of these antibodies discriminates GD from other causes of gestational hyperthyroidism [4].

Beyond their diagnostic utility, the determination of these antibodies has clear prognostic significance for the fetus. In fact, TRAbs can cross the placenta and induce abnormal fetal thyroid gland stimulation, similar to that occurring in the mother [14-15]. In general, the risk of fetal or neonatal thyrotoxicosis is greater in infants born to mothers with GD of recent onset, in whom TRAbs titers are usually higher than in those with less recent illness or in those who previously underwent ablative therapy (radioiodine or thyroidectomy) . The latter, however, may have TRAb titers persistently elevated even long after ablative therapy, and the recommendation is to measure maternal TRAbs in early pregnancy in these women. In all circumstances, namely current or past history of GD, if high TRAb titers (> 5 IU/L or 3 times the upper limit of normal) in the first trimester are found, TRAbs measurement should be repeated at weeks 18–22, and once again in late pregnancy (weeks 30–34), if elevated at mid gestation [4]

Complication of Graves disease in Pregnancy

Untreated or inadequately treated hyperthyroidism in pregnancy is associated with an increased risk of severe adverse effects for both mother and her fetus table-2[16-18] It should also be noted that an increased risk of thrombosis, apparently reversible with control of hyperthyroidism, has recently been reported in endogenous hyperthyroidism[19] a high level of suspicion should be maintained to allow for early detection of venous thromboembolism ,and prophylactic measure may have to be considered.

Table 2 Maternal---foetal impact of hyperthyroidism.

Maternal adverse effect	Foetal adverse effects
Gestational hypertension	Fetal loss(miscarriage and still birth)
Preeclampsia and eclampsia	Premature birth
Cardiac arrhythmia	Placental abruption
Cardiac failure	Intrauterine growth retardation
Thyroid storm	Accelerated bone maturation
Venous thrombosis	Fetal and neonatal thyrotoxicosis
	Central congenital hypothyroidism

Treatment of Graves' disease in Pregnancy

As is well known, there are three potential therapeutic approaches to GD in non-pregnant women: I 131, surgery, or medical treatment with ATDs. Of these three options, the administration of I131is contraindicated in pregnancy because of the risk of malformation, 7 and options are therefore limited to thyroidectomy or the use of ATDs

Antithyroid drugs. are the mainstay of treatment for Graves disease. Thionamide anti thyroid drugs Propyithiouracil(PTU) and Methimazole (MM) as well as its precursor carbimazole (CM) are widely used to treat thyrotoxicosis in pregnancy. All ATDs are equally effective in controlling hyperthyroidism during pregnancy. However they cross the placenta and may cause birth defects in off- spring when used in early pregnancy. However the patterns of associated birth defects are different. PTU mainly associated with urinary system defect and face and neck region malformation while Carbimazole/Methimazole is associated with a characteristic severe embryopathy, including choanal atresia, tracheoesophageal fistula, patent vitellointestinal duct, nipple abnormalities, aplasia cutis, dysmorphic facies, and cardio-vascular malformation. Birth defects associated with PTU appear to be less severe and overall risk is low as associated with Carbimazole/Methimazole. The critical period when maternal use of ATDs increases the risk of birth defects in offspring is 5-10 weeks of gestation.[20]

PTU is also associated with rare but severe fulminant hepatic failure both in nonpregnant population and in pregnant women.[24] with prevalence rates ranging from 0.1% to 0.5% and a high mortality rate (25---50%)[16,25] Cases of neonatal hepatitis in newborns born to mothers who had been treated with PTU have even been reported[26]

In the view of above birth defects and liver toxicity the choice of ATDs in pregnancy demands careful consideration taking an account of severity of thyrotoxicosis gestational age and the patient view. As the risk of obstetric complication with subclinical hyperthyroidism is minimal, pregnant women with subclinical hyperthyroidism due to GD do not need treatment with antitjyroid drugs. in addition if a women with stable GD who is euthyroid on a small dose of anti thyroid drug becomes pregnant, she should be assessed whether it is safe for her to avoid Anti thyroid drugs in the critical period of 5-10 weeks gestation .If an anti thyroid drug is considered necessary PTU has been recommended.

For this reason, the American Thyroid Association set out criteria for the use of PTU in the general population and in pregnant women[27] For pregnancy, the ATA recommended PTU in the first trimester of pregnancy and after 12 of pregnancy PTU should be discontinued because of the risk of liver disease, and MM/CM should be started. Outside pregnancy, the use of PTU is only recommended in two circumstances: first, if thyroid storm occurs, and second, in the presence of adverse effects induced by MM/CM.

Clinical management

As discussed above, treatment of GD during pregnancy should consist of PTU in the first trimester and MM/CM thereafter. The starting dose may range from 50 to 300 mg/day of PTU in three divided doses, 5 to 15 mg/day of methimazole, or 10 to 15 mg/day of carbimazole as a single dose[8] An attempt should always be made to use the lowest possible dose to avoid fetal hypothyroidism and goiter. Beta-blockers should only be used transiently, because their long-term use has been associated with intrauterine growth retardation, bradycardia, and neonatal hypoglycemia. Moreover, some authors have reported increased miscarriage with combined propranolol and ATD treatment.

Thyroid function should be monitored closely (every 4 weeks) to adjust the dose of ATDs with an aim to keep maternal free T4 level towards the upper end of the reference range.TSH concentration should not be used to guide dose adjustment. It is usually possible to decrease the dose of ATDs in the later part of pregnancy, and indeed a significant proportion up to 20-30% will be able to stop the drug altogether by the mid-second or third trimester. The use of a combined scheme (ATDs and THs) for the treatment of GD is absolutely contraindicated in pregnancy because it causes fetal hypothyroidism [8,28]

Surgery.

As regards the use of surgery to control GD in pregnant women, the different consensuses and clinical guideline [8,28] agree in recommending it only if the following occur:

1. Adverse reaction to ATDs which prevent their use.
2. The need for high ATD doses.
3. Patient non compliance with medical treatment.

In addition, Italian guidelines[28] also recommend surgery for cases of extensive maternal goiter with airway compression. If performed, the best time for surgery is from the second trimester onwards. This warrants the use of beta-blockers and sodium iodide (50---100 mg/day) for a short time period (10---14 days) in pregnant women with GD as a preparation for surgery. As discussed above, long-term treatment with beta-blockers should be avoided. Caution should also be taken when potassium iodide is administered to prevent the development of goiter and/or fetal hypothyroidism

Breast feeding and Antithyroid drugs

Anti thyroid drugs can be used to treat thyrotoxicosis in lactating mothers. Both carbimazole/methimazole and propylthiouracil are secreted in small amounts in milk and methimazole doses up to 20 mg daily (or propylthiouracil doses up to 300 mg daily) during breast feeding is thought not to affect infant thyroid function significantly [31]. A case-control study found that infants breast fed by thyrotoxic mothers with methimazole up to the daily dose of 20-30 mg have no impaired physical or neuropsychological development at age 48 to 86 months.[32] .In view of the association of the liver toxicity with propylthiouracil,carbimazole/methimazole is the preferred antithyroid drug for lactating women. The drug should be taken in smaller divided doses ,and just after breastfeeding .If high doses of antithyroid drug are required to control thyrotoxicosis in a lactating mother,the infant thyroid function should be monitored.

Preconception Counselling For Women with Graves Disease Planning Pregnancy

It is important that all women of reproductive age diagnosed with Graves disease are given information about issues relating to the management of the condition in pregnancy, including the association between the use of anti thyroid drugs in early pregnancy and birth defects in offspring. Women with overt thyrotoxicosis should be advised to delay conception until thyrotoxicosis is controlled. Also, women should be informed about the need of regular medical visits and serial thyroid blood tests during pregnancy, as well as about the risks of uncontrolled hyperthyroidism on pregnancy. If the women chooses ATDs to control thyrotoxicosis before pregnancy, propylthiouraci (PTU) is the preferable antithyroid drug..If the women becomes pregnant on anti thyroid drugs, the thyroid

function must be checked as soon as pregnancy is confirmed to to ascertain if she needs to continue the drugs or adjust the dose.[4].

Women on medical therapy with poorly controlled hyperthyroidism even on high doses of ATDs, should be considered for a definitive therapy for hyperthyroidism prior to conception. Both thyroidectomy and radioactive iodine ablation (RAIA) are effective means of permanently controlling hyperthyroidism, and the choice between the two modalities is mostly influenced by coexisting medical conditions and patient preference. In the setting of hyperthyroidism during pregnancy, additional specific considerations should be made. In particular, while the majority of patients with GD after surgical therapy experience a gradual decrease in circulating TRAbs, a transient increase in TRAb titers after RAIA may occur, with TRAb levels remaining persistently elevated for months to years [29]. A very recent study showed the incidence of neonatal hyperthyroidism to be 8.8% and 3.6% among the newborns born to mothers with GD who conceived within 6–12 months and 18–24 months after RAI, respectively [30]. This being the case, women with very elevated TRAb levels prior to conception should be better addressed to thyroidectomy than to RAIA, as TRAb levels tend to decrease more rapidly (within months to one year), and only rarely remain elevated for years. In any case, following either surgery or RAIA women should be advised to measure TRAbs and TSH prior to conception, and to avoid pregnancy if TRAbs are still high or if TSH is elevated (> 2.5 mU/L) on levothyroxine therapy.

CONCLUSIONS

Management of hyperthyroidism during pregnancy requires close maternal and fetal surveillance. Thyroid hormone excess is a risk factor for obstetrical and fetal complications and should be adequately controlled throughout pregnancy. However, because of the potential hazard to the fetus with the use of ATDs during pregnancy, special care should be taken to avoid both untimely or excessive fetal exposure to these drugs. Maternal hyperthyroidism due to GD poses the fetus at risk of hyperthyroidism because maternal antibodies enter the fetal compartment and may exert their effect on fetal thyroid. Women of reproductive age with GD should be routinely offered preconception counseling, and pregnancy should be postponed until hyperthyroidism is adequately controlled. Importantly, high maternal TRAb levels may even persist for years beyond resolution of hyperthyroidism in women definitively treated for GD by radioiodine or surgery, which requires measurement of TRAb prior to or upon becoming pregnant also in women with past history of GD. Although rarely, offspring of mothers with GD may develop fetal/ neonatal hyperthyroidism, the management of which requires close collaboration between endocrinologists, obstetricians, and neonatologists.

There are currently some critical issues in the therapeutic management of pregnant hyperthyroid women that need to be addressed. These include the identification of upper free-T4 cut-off values that may confidently be considered safe for the fetus, as some evidence has been provided showing that maternal free-T4 concentrations even within the higher end of the normal range might have detrimental effects on child neurodevelopment [33]. Also, further studies evaluating the safety of alternative therapies for hyperthyroidism in pregnancy (i.e., potassium iodide) are advisable, as current evidence suggests the use of both MMI and PTU to be associated with an increased risk of embryopathies

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