

**Review Article (Open access)**

## Thyroid Dysfunction during Pregnancy: A Review of the Current Guidelines

**Mustafa Al Abousi\***

Department of Endocrinology, Shatti Al-Qurum Medical center, Oman

**ABSTRACT-** Thyroid disease commonly affects women of childbearing age and is the second most common endocrinological disorder diagnosed in pregnancy after gestational diabetes. In normal gestation, the thyroid gland adapts its structure and function to satisfy increasing functional demand. The marked physiological changes that occur during normal pregnancy make it necessary to use specific reference ranges in the interpretation of thyroid function tests. It is well documented that thyroid disorders are associated with maternal and fetal complications during gestation, and its deleterious effects can also extend beyond pregnancy and delivery. Available epidemiological data report widely varying prevalence rates of thyroid disorders during the antenatal period. However, the need for universal thyroid screening remains controversial. Subclinical thyroid dysfunction is very frequent but easily missed without specific screening programs. Furthermore, appropriate management is crucial to prevent adverse maternal and fetal outcomes. Despite the correlation between thyroid function during pregnancy and maternal and fetal outcomes is a widely discussed issue, it remains important to clarify several points regarding screening, diagnosis, and treatment of thyroid dysfunction in pregnant ladies. In this article we try to discuss the physiological changes of the thyroid gland to meet the challenges of increased metabolic demands during pregnancy and focusing on pathological function changes; we also try to summarize the best way of screening, diagnosis, and treatment of thyroid dysfunction during pregnancy to improve maternal and fetal outcomes.

**Key Words:** Pregnancy, Thyroid gland, Hypothyroidism, Hyperthyroidism, Thyroid stimulating hormone

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### INTRODUCTION

Pregnancy has a profound impact on thyroid function. The thyroid increases 10% in size during pregnancy in iodine replete countries and by 20-40% in areas of iodine deficiency. Production of Thyroxine (T4) and Triiodothyronine (T3) increases by 50%, along with a 50% increase in the iodine daily requirement. These physiological changes are important to cope with an increase demand on thyroid gland during pregnancy (1).

Thyroid disease is second to diabetes mellitus as the most common endocrinopathy that occur in women during their

reproductive years. Symptoms of thyroid disease often mimic common symptoms of pregnancy, making it challenging to identify. Poorly controlled thyroid disease is associated with adverse outcomes during pregnancy, and treatment is an essential part of prenatal care to ensure maternal and fetal well-being (2).

### **Thyroid function tests (TFT) interpretation in pregnancy:**

To meet the challenges of increased metabolic demands during pregnancy, thyroid gland adapts several normal physiological changes in hormone synthesis and hypothalamic-pituitary-thyroid axis regulation. Consequently, TFT results of healthy pregnant women differ from those healthy non-pregnant women (Table 1) (3).

#### **\*Address for Correspondence:**

Mustafa Al Abousi

Endocrinologist

Department the Endocrinology

Shatti Al-Qurum Medical Center- Oman

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**Table 1:** Thyroid Function Test in Pregnancy

Physiological changes	Thyroid function test changes
↑ Thyroid binding globulin (TBG)	↑Serum total T3,T4 levels
First trimester hCG elevation	↑FT4 & ↓ TSH
↑ Plasma volume	↑T4 & T3 pool size
↑ Type III deiodinase due to hormone placental	↑T4&T3 degradation resulting in ↑ requirement
Thyroid enlargement in some women	↓ Serum thyroglobulin
↑ Iodine clearance	↓ Hormone production in iodine deficit areas

During pregnancy, reference ranges for TSH are lower because of the cross reactivity of the alpha subunit of hCG with the TSH. The American Thyroid Association guidelines 2011 recommended trimester-specific reference ranges, as defined in population with optimal iodine intake. If trimester-specific reference ranges are not available in the laboratory, the following reference ranges are recommended as shown in Table.2 (1,4).

Changes in binding -serum protein level can influence measurement of FT4 that rely on estimates rather than direct measurements resulting in inaccurate reported values (1,4).

**Table 2:** Trimester – specific ranges for TSH and T4

Test	Non-pregnant	1 <sup>st</sup> trimester	2 <sup>nd</sup> trimester	3 <sup>rd</sup> trimester
<b>TSH</b> mIU/L	0.3-4.3	0.1-2.5	0.2-3	0.3-3
<b>FT4</b> ng/dL	0.8-1.7	0.8-1.2	0.6-1	0.5-0.8
<b>TT4</b> mcg/dL	5.4-11.7	6.5-11.1	7.5-10.3	6.3-9.7

**Thyroid screening in pregnancy**

Endocrine society recommends screening only pregnant women at high risk of thyroid diseases using serum TSH measurement in Table 3 (Endocrine Society, 2012).

**Table: 3** Indications for thyroid screening in pregnancy

-Current thyroid therapy
-Goitre
-Family history of autoimmune thyroid diseases
-Personal history of:
Autoimmune disorder
High –dose neck radiation
Previous delivery if infant with thyroid disease
Postpartum thyroid dysfunction
Therapy for hyperthyroidism
Type 1 D.M

**Hypothyroidism: Maternal and Fetal Aspect**

The incidence of hypothyroidism during pregnancy is estimated to be 2-3% for subclinical hypothyroidism, and 0.3-0.5% for overt hypothyroidism (5). It would be anticipated that such percentage would be higher in areas of iodine insufficiency. In iodine –sufficient region, the most common causes of hypothyroidism are autoimmune thyroiditis and iatrogenic hypothyroidism after treatment of hyperthyroidism (6). Overt hypothyroidism (OH) is defined as TSH>2.5 mU/L and low FT4, or TSH equal to 10 or above irrespective of FT4 levels.

On the other hand, subclinical hypothyroidism (SCH) is defined as TSH between 2.5–10 mU/L and normal FT4 (1). Both overt hypothyroidism and subclinical hypothyroidism have adverse effects on the course of pregnancy and fetal development (7). On another hand, isolated hypothyroxinemia (low FT4 + normal TSH) has been found not to be associated with adverse perinatal outcomes Table 4 (8).

**Table 4:** Hypothyroidism and Pregnancy –Maternal and Fetal complications

Condition	Preconception	Pregnancy	Postpartum
Overt Hypothyroidism (OH)	Decreased infertility, Increased abortion	Abortion, Preterm birth, Low birth weight, Fetal death, Gestational hypertension, Placenta Abruption, Preeclampsia, Fetal neurocognitive deficits	Postpartum haemorrhage, Maternal thyroid dysfunction
Subclinical Hypothyroidism (SCH)	Similar to over hypothyroidism but less documentation exists.		

A large amount of retrospective and case-controlled studies confirmed the detrimental effect of overt hypothyroidism on pregnancy and fetal health. Moreover, many data provide circumstantial evidence supporting an increased risk of adverse outcomes from maternal subclinical hypothyroidism. Table 5 summarized some of these trial's results.

**Table: 5** Summary of some trials demonstrated adverse effects of overt hypothyroidism (OH) & subclinical hypothyroidism (SCH) on pregnancy outcomes

	Albalovich <i>et al.</i> (9)	Leung <i>et al.</i> (10)	Negro <i>et al.</i> (11)	Benhadi <i>et al.</i> (12)	Casey <i>et al.</i> (13)	Ashoor <i>et al.</i> (14)
<b>Type</b>	OH	OH	SCH	SCH	SCH	SCH
<b>Results</b>	60% risk of fetal loss in untreated overt hypothyroidism in pregnant women	22% risk of gestational hypertension in women with overt hypothyroidism	Significant reduction in a combined end points of pregnancy complications in treated women with TSH >2.5Mu/l in both TPOAb positive or negative SCH	Increased risk of child loss with higher TSH	2-3 folds increased risk of pregnancy related complications in untreated women	Increased risk of abortion and fetal death in untreated women with TSH above 97.5 <sup>th</sup> percentile and FT4 below 2.5 <sup>th</sup> percentile

Either to due iodine deficiency or autoimmune thyroid disease, a reduction of circulating of maternal thyroxine has been shown to result in lower I.Q in infants in retrospective (15) and prospective (16) studies. However, results from Controlled Antenatal Thyroid Screening (CATS) study suggest a caution and a degree of uncertainty relating to this approach (17). The results of the second wave of the controlled Antenatal Thyroid Screening (CATS II), which is an extensive study, are still pending (18).

L-T4 therapy is the mainstay of treatment for maternal hypothyroidism (2). The aim of treatment to normalize maternal serum TSH values within trimester-specific pregnancy reference range Table 1. It is strongly recommended not to use of T/T3 combination or desiccated thyroid during pregnancy (1).

All overt hypothyroidism cases should be treated during pregnancy. Women who have a TPOAb positive subclinical hypothyroidism, treatment should be considered.

However; there is insufficient evidence to recommend for or against universal treatment of TPOAb negative women with subclinical hypothyroidism (1).

When a woman with hypothyroidism gets pregnant, the preconception L-T4 dose should be increased, and may require up to a 30-50% increment, as soon as possible to ensure that TSH <2.5 mU/L (19)

Serum TSH and FT4 should be measured every 4-6 weeks until 20 weeks` gestation and until the patient on stable medication dose; it should be measured again at 24-28 weeks and 32-34 weeks` gestation (20).

After delivery, L-T4 should be decreased to the prepregnancy dosage over a four- week period, and further adjustment should be guided by TSH levels 4-6 weeks after delivery (1).

### Hyperthyroidism and pregnancy

In general, hyperthyroidism is less common than hypothyroidism, with an approximate incidence during pregnancy of 0.2% (5). In the first trimester of normal pregnancies, TSH levels usually are suppressed due to a stimulatory effect of hCG on the TSH receptors (21); therefore a suppressed TSH should be evaluated in conjunction with serum FT4. The diagnosis of hyperthyroidism is confirmed by suppressor undetectable TSH and an elevated FT4 (1). Grave`s disease accounts for 90% of hyperthyroidism (22) along with other causes Table 6.

**Table 6:** Etiology of hyperthyroidism in pregnancy

Nodular goitre or Toxic solitary adenoma
Gestational trophoblastic disease
Viral thyroiditis
Pituitary tumors–Secondary Hyperthyroidism
Ovarian tumors

Transient hyperthyroidism may also be associated with hyperemesis gravidarum and gestational hyperthyroidism (23). No prior history of thyroid disease, absence of eye sings or goitre favour the diagnosis of gestational hyperthy-

roidism rather than Grave`s disease. TRAb level can be diagnostically useful in doubtful cases (24). Supportive therapy is an appropriate management in gestational hyperthyroidism (25).

The natural history of hyperthyroid disorders varies with the underlying aetiology. Grave`s disease is typically characterized by an initial exacerbation in the first trimester thought to be caused by the additive stimulatory effect of hCG on thyroid gland. Symptoms usually improve during the second trimester, only to worsen again in postpartum period (5).

Overt hyperthyroidism that is inadequately treated is associated with a detrimental effect on maternal and neonatal outcomes (26) Table 7.

According to study by Casey BM et al 2005 (13), a more than 25000 women with subclinical hyperthyroidism have been studied. It has been shown no increment in adverse pregnancy outcomes; therefore, treatment is not recommended in these cases.

**Table 7: Hyperthyroidism and Pregnancy- Maternal and Fetal complications**

Condition	Preconception	Pregnancy	Postpartum
Overt Hyperthyroidism	Congenital malformation	Fetal: goitre, IUGR, small for gestational age, stillbirth, thyroid dysfunction Maternal: Preterm delivery, preeclampsia, placental abruption, thyroid storm, congestive heart failure (27)	Neonatal thyroid dysfunction, neonatal goitre
Subclinical hyperthyroidism	–	none	–

Hyperthyroidism during pregnancy is treated with anti-thyroid drugs (28). Because Methimazol is associated with birth defects such as aplasia cutis and choanal or oesophageal atresia (29). Propylthiouracil is a preferred drug during first trimester (30). However, it is recommended to switch to Methimazol after the first trimester because of the risk of hepatotoxicity associated with Propylthiouracil use (31).

The essential practical aspect of Grave's hyperthyroidism management during pregnancy should include:

Discuss treatment-related issues with patients such as effect on patient, effect on fetus, and breast feeding.

Start propylthiouracil –use for the first trimester.

Render patient euthyroid-continue with low dose carbomazol or methimazole to ensure a serum FT4 level at or moderately above reference range (1).

Serum FT4 and TSH levels should be monitored every 2-6 weeks.

Women with active Grave's disease, a history of Grave's disease treated with radioactive iodine or thyroidectomy, or a history of delivering an infant with hyperthyroidism should checked for TRAb at 24-28 weeks gestation (32).

In women at high risk , including those with uncontrolled hyperthyroidism or high TSH receptor antibodies (TRAbs) titre, fetal surveillance and ultrasonography should be performed monthly after week 20 gestation to detect evidence of fetal thyroid dysfunction( e.g goitre, hydrops, growth restriction, heart failure (33).

Inform paediatrician, Check infant for thyroid dysfunction if indicated, & Review postpartum-check for exacerbation.

In the same line, ablation therapy with RAI is contraindicated in pregnancy and lactation. Thyroidectomy is rarely considered in second trimester in cases with ATDs side effects, requiring a higher ATDs dose, or non-complaint with drug therapy (1).

### **Postpartum Thyroid Dysfunction:**

Postpartum thyroiditis is the most common cause of postpartum thyroid dysfunction, which affects 1.1% -21.1% of women (34). Patients with Type 1 diabetes and women with high TPOAb or TgAb titres are at increased risk of postpartum thyroiditis (35). The clinical course of postpartum thyroiditis varies (1) as approximately 25% of patients present with hyperthyroidism, followed by hypothyroidism, and then recovery.

Furthermore, 43% of patients with postpartum thyroiditis present with symptoms of hypothyroidism and 32% may present with hyperthyroidism (1).

Practically speaking, treatment of hyperthyroidism is generally symptomatic using B-blockers and no role for ATD. In contrast, postpartum hypothyroidism should be treated with levothyroxine in symptomatic (36). Women with history of PT are at increased risk of permanent hypothyroidism and should be screened annually then after (37).

### **CONCLUSIONS**

There is a consensus that pregnancy imposes a stress on the thyroid which is greater in iodine –deficit areas. All women with thyroid disorders should counsel about the importance of achieving euthyroidism before conception to avoid poor outcomes. Hypothyroidism is more common than hyperthyroidism, and both required appropriate management to improve maternal and fetal outcomes.

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