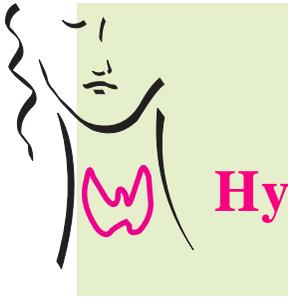


Managing Hypothyroidism



Hypothyroidism

Hypothyroidism is the most common disorder of thyroid function. It is reported to be more common in women than in men. In hypothyroidism, there is decreased production and secretion of the thyroid hormones by the thyroid gland.

The principal role of the thyroid gland is to regulate tissue metabolism through production of the thyroid hormones thyroxine (T_4) and in smaller amounts tri-iodothyronine (T_3). In infants and children thyroid hormones are also needed for normal growth and development.

Hypothyroidism can be classified on the basis of aetiology, age of onset and on the basis of its severity. The coming pages of this section provide detailed discussion about classification of hypothyroidism.

Aetiology - Hypothyroidism can be classified on the basis of aetiology as primary, secondary or transient.

a) **Primary Hypothyroidism**

This is hypothyroidism caused by disorders of the thyroid gland itself.

Causes:

- Destruction of thyroid tissue
 - Chronic autoimmune thyroiditis
 - goitrous
 - atrophic
 - Post thyroidectomy
 - Post radioactive iodine therapy for thyrotoxicosis
 - Neck radiation
- Iodine deficiency
- Disorders of hormone synthesis-enzyme defects
- Antithyroid agents, lithium, iodine, radiocontrast dyes containing iodine, amiodarone

The commonest cause of primary hypothyroidism in iodine-sufficient areas is chronic autoimmune thyroiditis and in iodine-deficient areas - iodine deficiency itself.

b) Central / Secondary Hypothyroidism

Decreased thyroid hormone production and secretion by the thyroid gland due to inadequate stimulation by thyroid stimulating hormone (TSH) because of pituitary or hypothalamic disorders.

Causes:

- Pituitary disorders - decreased TSH
- Hypothalamic disorders-decreased Thyrotropin Releasing Hormone (TRH)

c) Transient Hypothyroidism

In this type, there is decreased thyroid hormone production and secretion for a transient period of time.

Causes:

- Silent thyroiditis
- Postpartum thyroiditis
- Subacute thyroiditis
- After withdrawal of thyroid hormone therapy in euthyroid patients

Age of onset: Hypothyroidism is also classified on the basis of age of onset as

- Congenital hypothyroidism
- Cretinism
- Juvenile hypothyroidism
- Adolescent hypothyroidism
- Adult hypothyroidism.

a) Congenital Hypothyroidism

Causes:

Congenital Hypothyroidism

Transient	Permanent
<ul style="list-style-type: none">● Iodine deficiency	<ul style="list-style-type: none">● Thyroid dysgenesis
<ul style="list-style-type: none">● Iatrogenic	<ul style="list-style-type: none">● Maternal exposure to ^{131}I
<ul style="list-style-type: none">● Maternal/neonatal	<ul style="list-style-type: none">● Dyshormonogenesis
<ul style="list-style-type: none">● Iodine deficiency maternal RAI therapy	<ul style="list-style-type: none">● Congenital toxoplasmosis
<ul style="list-style-type: none">● TSH receptor blocking antibodies	<ul style="list-style-type: none">● Hypothalamic pituitary disorders
<ul style="list-style-type: none">● Idiopathic	

This type of hypothyroidism has been in existence since antiquity. This was portrayed in the ancient sculptures of goitrous dwarfs in 400 BC in South America. It was also described in writings about goitre in ancient Roman empire in the first century.

Congenital hypothyroidism presents at birth. It may be transient or permanent.

b) Cretinism

Severe iodine deficiency causing hypothyroidism in infancy and presenting as mental retardation, neurological maldevelopment and impaired growth is called cretinism. The infant having this form of hypothyroidism is called a cretin. It is rightly stated about a cretin that “What was supposed to be made into the image of God, has turned into an Imp”.

- Epidemiology

It is associated with endemic goitre and severe iodine deficiency.

- Clinical manifestations

These consist of mental deficiency, together with either of the following :

- i) predominant neurological syndrome - which consists of disorders of stance and gait and disorders of hearing and speech.

ii) predominant hypothyroidism and stunted growth

- *Prevention*

Prevention of endemic cretinism with adequate correction of iodine deficiency.

c) Juvenile Hypothyroidism

Occurs in childhood and manifests mainly as growth retardation along with other generalised features of hypothyroidism

d) Adolescent Hypothyroidism

Hypothyroidism during adolescence presents with delayed puberty with/without short stature and menstrual irregularities in females.

Severity : Hypothyroidism is also classified on the basis of severity as

- subclinical hypothyroidism
- overt or frank hypothyroidism

a) Subclinical Hypothyroidism

In this, patients are asymptomatic and are identified in screening especially in patients at risk. Spontaneous subclinical hypothyroidism is more common in women and the incidence increases with age and is associated with the presence of antithyroid antibodies.

b) Overt or Frank Hypothyroidism

All causes of hypothyroidism can manifest with moderate to severe symptoms and signs. However, the clinical manifestations are variable and sometimes nonspecific too.



Risk Factors

The risk of hypothyroidism does not remain the same across entire population. It changes depending upon sex, age and with presence or absence of other autoimmune disorders.

The following is the list of such factors which will serve as needle of 'suspicion' and may help in early diagnosis as well as treatment of hypothyroidism.

- Past history of thyroid / pituitary / hypothalamic disease.
- Family history of thyroid disease
- Elderly individuals
- History of hyperlipidaemia
- History of depression
- Obesity
- History of drug intake e.g. amiodarone, iodine, lithium carbonate, para-aminosalicylic acid

- History of other autoimmune diseases in the patients or in the family
 - insulin dependent diabetes mellitus
 - primary adrenal insufficiency
 - pernicious anaemia
 - vitiligo
 - malabsorption syndromes
 - collagen vascular disorders
- History of thyroid surgery
- History of RAI¹³¹ treatment for thyrotoxicosis
- History of head and neck irradiation
- History of postpartum thyroid dysfunction
- Down syndrome
- Short stature

These patients need to be screened for the presence of hypothyroidism. Clinical features discussed in the next section along with diagnostic criteria are to be utilised for confirmation of hypothyroidism.



Clinical Features

The clinical features of hypothyroidism are variable, many a times nonspecific. A high index of suspicion is necessary especially in patients who are at risk for developing hypothyroidism but still are subtle in their presentation.

The clinical features vary with age of onset and severity of hypothyroidism

I Clinical manifestations of hypothyroidism in general/in adults

- Fatigue
- Lethargy
- Mental impairment
- Depression
- Goitre
- Non-pitting oedema
- Menstrual abnormalities in women
- Repeated abortions in productive age of women.
- Cold intolerance
- Hoarseness of voice
- Dry skin
- Weight gain
- Arthralgias

II Hypothyroidism during adolescence

- Delayed puberty
- Growth retardation with delayed bone age
- Galactorrhoea
- Menstrual disorders in adolescent girls

III Hypothyroidism during childhood

- Dry skin, generalised myxedema
- Constipation
- Delayed dentition
- Growth retardation
- Delayed skeletal maturation
- Myopathy
- Precocious sexual development

IV Clinical manifestations of congenital hypothyroidism

● Early neonatal hypothyroidism

- Prolonged icterus
- Oedema
- Birth weight > 4 kg
- Post datism : gestation > 42 weeks
- Poor feeding, hypothermia
- Abdominal distension
- Large posterior fontanelle

● Onset during 1st month

- Peripheral cyanosis/mottling
- Respiratory distress
- Failure to gain weight
- Constipation
- Decreased activity

- Onset during first 3 months

- Umbilical hernia
- Constipation
- Hoarse cry
- Macroglossia
- Generalised myxedema
- Dry skin



End Organ Impact

Hypothyroidism can affect all systems of the body if not treated

a) Cardiovascular system

- Cardiac output is reduced but peripheral vascular resistance is increased. Diastolic blood pressure may be increased and pulse pressure decreased
- Heart may be enlarged and pericardial effusion may occur
- Sinus bradycardia, low amplitude 'p' wave ST segment alterations may be obvious on the ECG
- Angina pectoris can occur rarely

b) Central Nervous system

- Deficiency in foetal / neonatal life leads to maldevelopment of CNS which is irreversible
- All intellectual functions are decreased. Lethargy, somnolence prevail. Headaches are frequent

c) Skeletal system

- Impaired linear growth occurs
- Joint pain and stiffness
- In early life if hypothyroidism occurs epiphyseal dysgenesis is known to occur

d) Muscular system

- Stiffness and aching of muscles
- Slow muscle-stretch reflexes, muscle enlargement, or atrophy

e) Gastrointestinal system

- Appetite is decreased
- Gaseous distension of abdomen
- Constipation
- Rarely ascites is present
- Achlorhydria and pernicious anaemia may be occasionally present

f) Renal system

- Decrease in GFR (Glomerular Filtration Rate)
- Hyponatraemia

g) Reproductive system

- Sexual development may be arrested or it may be precocious
- Decreased fertility or recurrent abortions
- In woman, decreased libido and anovulation are known to occur
- Menorrhagia, amenorrhoea
- In man there is decreased libido or impotence and/or oligospermia

h) Skin

- Myxoedematous appearance (thickened features and puffiness) due to accumulation of mucopoly-saccharides on dermis and other tissues
- Non-pitting oedema, localised - around the eyes, on legs/generalised.

- Enlarged tongue
- Dry, coarse ichthyotic skin
- Hair-dry and brittle
- Loss of scalp hair and/or lateral eyebrow hair
- Nails-brittle-break easily and grow slowly
- In central hypothyroidism these changes are not seen.

i) Haemopoietic system

- Microcytic/macrocytic anaemia can occur
- Capillary fragility is seen

j) Pituitary and adrenal

- Longstanding hypothyroidism causes increase in size of the thyroid gland
- Hyperprolactinaemia can be present
- Increased turnover of cortisol

k) Respiratory system

- Pleural effusion may occur in hypothyroidism, obstructive sleep apnoea is seen commonly

l) Ocular System

- Increased intraocular pressure

m) Metabolic system

- Low metabolic rate
- Increased lipids cholesterol, LDL cholesterol, and triglycerides

In the following section we will discuss the comorbidity associated with hypothyroidism



Hypothyroidism has been frequently associated with other diseases. These co-morbid states include infertility, menstrual irregularities, Type 1 diabetes mellitus, depression, obesity, hypercholesterolaemia, etc.

a) Hypercholesterolaemia

Impaired thyroid function may be the cause of a hypercholesterolaemia. Clinical studies have shown that hypothyroid patients have significantly elevated serum cholesterol levels - from about 30% to 50% above control values. Also increase in low density lipoprotein (LDL) cholesterol, modest fasting hypertriglyceridaemia has been observed in hypothyroid patients, particularly when they are obese.

b) Diabetes Mellitus

Approximately 10% of patients with Type 1 diabetes mellitus develop chronic thyroiditis in

their lifetime which may include the insidious onset of subclinical hypothyroidism. Insulin requirements may change in the presence of subclinical hypothyroidism. It is important to examine patients with diabetes for the development of a goitre.

c) Infertility

Some patients with infertility and menstrual irregularities have underlying subclinical or clinical hypothyroidism. In some patients with elevated TSH levels, thyroxine replacement therapy may normalize the menstrual cycle and restore normal fertility.

d) Depression

The diagnosis of subclinical or clinical hypothyroidism must be considered in suspected patients with depression. In fact, a small

proportion of all patients who are depressed have primary hypothyroidism - either overt or subclinical. Also all patients on lithium therapy need periodic thyroid evaluation because lithium may induce goitre and hypothyroidism.

e) Obesity

Some obese patients may have hypothyroidism. Caloric needs due to hypothyroidism may be responsible for weight gain in these persons.

In view of the strong association between hypothyroidism and the above comorbid states, it is advisable to look for hypothyroidism in these patients and screen accordingly through T_4 and TSH testing.



I Clinical Criteria

- History taking to evaluate patients at risk
- Symptoms/signs of thyroid hormone deficiency
- Evidence of disease/previous treatment or exposure known to cause thyroid/pituitary/hypothalamic failure
- Conditions associated with increased risk of chronic autoimmune thyroiditis

II Laboratory Testing

Specific tests

Include measurement of TSH, T_4 or FT_4
(Free T_4), T_3 or, FT_3 (Free T_3)

In primary hypothyroidism

Decreased T_3 , T_4 levels with elevated TSH or
Normal T_3 low T_4 and high TSH / Low T_3 occurs
in severe cases

In subclinical hypothyroidism

Normal T_3 , T_4 levels with elevated TSH levels

In central hypothyroidism

Low T_3 , and T_4 levels with normal or low TSH

T_3 , T_4 , TSH Levels

T_3 , T_4 , Normal TSH Normal	T_3 , T_4 , Normal TSH High	T_3 , T_4 , Low TSH High or	T_3 , T_4 , Low TSH Normal or
		T_3 , Normal T_4 Low TSH High	T_3 , T_4 , Low TSH Low
Normal	Subclinical Hypothyroidism	Primary Hypothyroidism	Central Hypothyroidism

In autoimmune thyroid disease causing hypothyroidism antimicrosomal antibodies are present in 90% of patients.

Neonatal screening for congenital hypothyroidism was introduced in 1974. This has improved the prognosis of patients with congenital hypothyroidism.

Ideally, screening should be done with T_4 and TSH

levels by 4th day of neonatal life and reconfirmed by with following values

$FT_4 < 6\mu\text{g/dl}$ and $TSH > 20\text{-}40 \mu\text{ I U /L}$

In case of central hypothyroidism

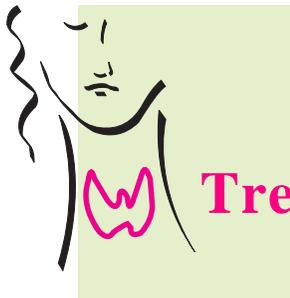
- MRI brain and pituitary
- Other hormonal evaluation

Typical reference ranges for Serum Thyroid Hormones and TSH*

TSH	0.3 - 4.0 mu/L
Free T ₄	0.7 - 2.1 ng/dL
T ₄	4.0 - 11 μg/dL
Free T ₃	0.2 - 6.5 ng/dL
T ₃	75 - 175 ng/dL

* Reference ranges may vary according to laboratory

Early diagnosis can be a major step forward in the treatment of hypothyroidism. In the next section we will discuss the treatment of hypothyroidism.



Treatment

Historically, hypothyroidism is the first endocrine disorder to be treated by supplementation of the deficient hormone.

- It was treated with animal thyroid extracts in the past
- This was followed by development of purified thyroid hormone preparations.

Available thyroid hormone preparations are

- Thyroxine sodium (T_4)
- Tri-iodothyronine (T_3)
- Combination of synthetic T_3 and T_4
- Thyroid USP (desiccated animal thyroid containing T_3 and T_4 in the form of thyroglobulin)

The mostly widely used and preferred preparation is synthetic T_4 , thyroxine sodium.

Goal of treatment

To normalise the thyroid hormone status in peripheral tissues.

Initiation of therapy

Initial dosage may be based on

- Age of patient
- Severity and duration of hypothyroidism
- Presence of associated disorders like ischaemic heart disease, adrenal insufficiency

Paediatric hypothyroidism

- The dosage of thyroxine sodium for paediatric hypothyroidism varies with age and body weight. Thyroxine should be given at a dose that maintains the serum total T_4 or free T_4 concentrations in the upper half of the normal range and serum TSH in the normal range.
- Thyroxine sodium therapy is usually initiated at the full replacement dose. Infants and neonates with very low or undetectable serum T_4 levels

(< 5 mcg/ dL) should start at the higher end of the dosage range (e.g. 50 mcg daily).

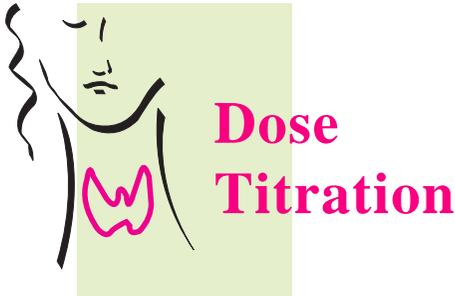
- A lower starting dosage (e. g. 25 mcg daily) should be considered for neonates at risk of cardiac failure, increasing every few days until a full maintenance dose is reached.
- In children with severe, long-standing hypothyroidism, thyroxine sodium should be initiated gradually, with an initial dose of 25 mcg for two weeks, and then increasing the dose by 25 mcg every 2 to 4 weeks until the desired dose based on serum T₄ and TSH levels is achieved.

Age	Daily dose per kg. Body weight*
0 - 3 mos	10 - 15 mcg
0 - 6 mos	8 - 10 mcg
6 - 12 mos	6 - 8 mcg
1 - 5 yrs	5 - 6 mcg
6 - 12 yrs	4 - 5 mcg
> 12 yrs	2 - 3 mcg
Growth and puberty complete	1.6 mcg

* To be adjusted on the basis of the clinical response and laboratory test

Adults

- Young, healthy adults with no cardiac/respiratory disease are started with 1.6 mcg/kg/day of thyroxine sodium administered once daily.
- In elderly patients or in younger patients with cardiovascular disease dose required is lower than the usual adult dose i.e. <1mcg/kg/day, administered once a day. To start with in elderly patients 12.5 to 50 mcg of thyroxine sodium are given daily and increment of 12.5 to 25 mcg are made at 3-6 week intervals if required.
- Women who are maintained on thyroxine sodium during pregnancy may require increased doses.
- Treatment of subclinical hypothyroidism, when indicated may require lower than usual replacement doses; (1mcg/kg/day). Patients for whom treatment is not initiated should be monitored yearly for changes in clinical status, TSH and thyroid antibodies.
- In patients with associated adrenal insufficiency, low doses of thyroxine sodium are started only after initial treatment with glucocorticoids.



The initial dose of thyroxine sodium administered depends on patient's age, on the severity and duration of the hypothyroidism and on the existence of the underlying cardiovascular disease.

The dosage needs to be titrated against TSH levels according to individual patient's needs.

The patient should be re-evaluated and the serum TSH level should be measured in about 6- 8 weeks. The dose of thyroxine should be increased if the serum TSH concentration is elevated and decreased if it is low. Individualization and titration of proper dose is critical, aiming at normalisation of serum TSH levels.

- If proper dosage adjustment is not done then under-treatment can lead to persistence and exacerbation of symptoms can lead to end organ damage, while over-treatment can lead to following side effects.

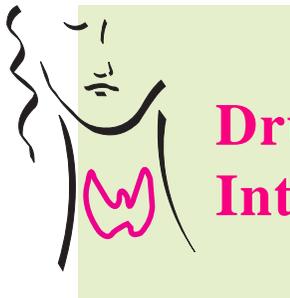
Side effects of over-treatment with thyroxine sodium

a) Children

- thyrotoxicosis due to thyroid hormone
- increased intracranial pressure
- craniosynostosis

b) Adults

- accelerates bone loss in postmenopausal women
- increased heart rate
- increased left ventricular wall thickness and contractibility



Drug Interactions

Factors influencing the requirements of thyroxine sodium treatment

I Increased requirement

- Pregnancy

II a) Drugs leading to decreased absorption of thyroxine

- Sucralfate
- Aluminium hydroxide
- Ferrous sulphate

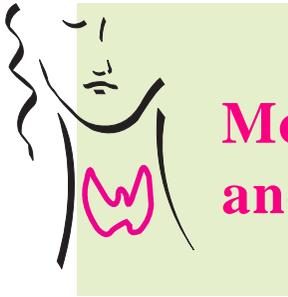
b) Drugs leading to increased clearance of thyroxine

- Rifampicin
- Carbamazepine
- Phenytoin

c) Drugs that prevent conversion of T_4 to T_3

- Glucocorticoids
- Amiodarone

Depending on the above factors dose of thyroxine sodium may need adjustment.



Monitoring and Follow up

Hypothyroidism needs life long treatment & patient compliance can be an issue hence monitoring & follow up are important

Adults:

- Titration of dosage of thyroxine is done to maintain TSH in normal range of 0.2-5 μ IU/L and in cases of central hypothyroidism to maintain T_4 levels in normal range (5- 13.5 μ g/dl)
- Follow up of these patients is done with TSH testing at 6-8 weeks intervals
- In severe hypothyroid patients, older patients or in young patients with a history of a cardiovascular disease TSH testing is done at 3-6 weeks interval
- In central hypothyroidism FT_4 / T_4 testing at 4-6 week intervals

- Once the dose is titrated and TSH /T₄ maintained within normal limits, patient should be followed up at 6 months or yearly intervals

Infants and neonates:

- Serum T₄ and TSH measurements should be evaluated at the following intervals, with subsequent dosage adjustment to normalize serum total T₄ or FT₄ and TSH
- 2 and 4 weeks after the initiation of Thyroxine sodium treatment ;
- Every 1 to 2 months during the first year of life;
- Every 2 to 3 months between 1 & 3 years of age;
- Every 3 to 12 months thereafter until growth is completed

Evaluation at more frequent intervals is advisable when compliance is poor or abnormal values are obtained. Patient evaluation is also advisable approximately 6 to 8 weeks after any change in thyroxine sodium dose.



Myxedema coma occurs as an extreme manifestation of severe hypothyroidism seen in patients with long standing hypothyroidism that is untreated.

I Precipitating events

- cold months
- pulmonary events
- cerebrovascular accidents
- congestive heart failure
- metabolic derangements
- drugs - sedatives, narcotics, antidepressants

II Cardinal Features

- hypothermia
- unconsciousness
- other signs of hypothyroidism

III Treatment

- treatment of underlying cause
- ventilatory support
- correction of electrolyte imbalance
hypothermia, hypotension
- steroid treatment - injection hydrocortisone
100mg, 8 hourly parenterally during initial
7-10 days then tapered off
- once patient is stable, consider evaluation of
adrenal status

Thyroid Hormone Therapy (Thyroxine Sodium)

- Initial dose (loading dose), 100-500mcg
followed by maintenance dose of 50-100mcg/
day
- Parenteral preparations if not available
thyroxine tablets to be used through
nasogastric tube, 500-1000 mcg initial dose
followed by 50-100 mcg /day. Care to be taken
if patient has ischaemic heart disease

- Due to illness, T_4 given may not be converted to T_3 so some advise T_3 therapy

T_3 treatment: quick onset of action

- Bolus IV (Tri-iodothyronine) T_3 20mcg, followed by 10mcg of T_3 for first 24 hours and 10mcg 6 hourly for next 2-3 days then oral administration is started once patient is stable. However intravenous T_3 therapy is marked by large and unpredictable fluctuations in serum T_3 levels and is dangerous to the cardiac status.
- Some advocate combination of T_3 and T_4 treatment

References:

1. AACE Clinical Practice Guidelines for the Evaluation and Treatment of Hyperthyroidism and Hypothyroidism 5 January 1995.
2. Polikar R, Burger AG, Scherer U, Nicod P. The thyroid and the heart. *Circulation*. 1993; 87 (5): 1435-1441
3. Nemeroff CB. Clinical significance of psychoneuroendocrinology in psychiatry; focus on the thyroid and adrenal. *J Clin Psychiatry*, 1989; 50 (5, Suppl) 13:20
4. Vassilopoulou-Sellin R, Sellin JH. The gastrointestinal tract and liver in hypothyroidism. In Braverman LE, Utiger RD. eds. *Werner and Ingbar's The Thyroid*. 7th ed. Philadelphia, PA :Lippincott - Raven Publishers; 1996:816-820
5. Laycock MA, Pascuzzi RM. The neuromuscular effects of hypothyroidism. *Semin Neurol*. 1991; 11(3):288-294
6. Moses Am, Scheinman SJ. The kidneys and electrolyte metabolism in hypothyroidism. In : Braverman LE, Utiger RD, eds. *Werner and Ingbar's The Thyroid*. 7th ed. Philadelphia, PA: Lippincott-Raven Publishers; 1996:812-815
7. Emerson Ch. Thyroid function and disease in the female. In : Gold JJ, Joshimovich JB, eds. *Gynecologic Endocrinology*. 4th ed. New York, NY: Plenum Publishing Corp; 1987:109-133
8. Klausen IC, Neilsen FE, Hegedis L, Gerdes LU, Charles P, Faergeman O, Treatment of hypothyroidism reduces low-density lipoproteins but not lipoprotein (a). *Metabolism* 1992; 41 (8) ; 911-914.
9. Bernhard JD, Freedberg IM, Vogel LN. The skin in hypothyroidism. In : Braverman LE, Utiger RD, eds. *Werner and Ingbar's The Thyroid*. 7th ed. Philadelphia, PA:Lippincott-Raven Publishers; 1996:792-795
10. Centanni M, Cesareo R, Verallo O, et al. Reversible increase of intraocular pressure in subclinical hypothyroid patients. *Eur J. Endocrinol*. 1997; 136(6):595-598
11. Brent GA, Larsen PR; Treatment of Hypothyroidism. *The Thyroid*, ed. Werner and Ingbar, 1996,884

12. Essentials of Medical Pharmacology ed. KD Tripathi. 4th edition, 1998,254
13. Berger DN, Chopra IJ; Hypothyroidism. Conn's Current Therapy, ed RE Rakel,651.
14. Therapeutic Drugs. ed. Colin Dollery, 2 nd edition , 1999, 449
15. Larsen PR, Ingbar SH. The thyroid gland. In: Wilson JD, Foster DW, eds. Williams Textbook of Endocrinology, 8th ed. Philadelphia, PA: WB Saunders Co; 1992:357-487.
16. Utiger RD. Hypothyroidism. In: DeGroot LJ et al. eds. Endocrinology, Vol 1. 2nd ed. Philadelphia, Pa: WB Saunders Co, 1989: 702-721.
17. Roti E, Braverman IE. Thyroid hormone therapy: when to use it, when to avoid it. Drug Therapy. 1994;24(4): 28-35.
18. Stagnaro-Green A. Postpartum thyroiditis: prevalence, aetiology, and clinical implications, Thyroid Today, 1993;16:1-11.
19. Alvarez Marfany M, Roman SH, Drexler AJ, et al: Long-term prospective study of postpartum thyroid dysfunction in women with insulin dependent diabetes mellitus. J Clin Endocrinol Metab 1994; 79: 10-16.
20. Stockigt JR. Serum thyrotropin and thyroid hormone measurements and assessment of thyroid hormone transport, In: Braverman LE, Utiger RD, eds. Wener and Ingbar's The Thyroid, 7th ed. Philadelphia, PA : Lippincott - Raven Publisher's; 1996 : 377 - 396.