Thyroid Disorders

Practical Approach

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An Initiative By:

Pakistan Endocrine Society

PAKISTAN ENDOCRINE SOCIETY

Thyroid Disorders A practical approach

EDITED BY

Dr. Ibrar Ahmed
FCPS (Med), FCPS (Endocrine)
Assistant Professor
Department of Diabetes & Endocrinology
Lady Reading Hospital Peshawar.

Dr. Musarrat Riaz
FCPS (Med), FCPS(Endocrine)
Associate Professor
Baqai Institute of Diabetology &
Endocrinology, BMU

Pakistan Endocrine Society
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www.pakendosociety.org

CONTRIBUTORS

Dr. Aisha Sheikh
FCPS, FACE (USA) Fellowship Diabetes, Endocrinology & Metabolism (AKUH), PGDip Diabetes (UK), PGDip Endocrine (UK)
Consultant Endocrinologist & Faculty member (AKUH), Recognized tutor, University of South Wales,(UK)
President-elect of Pakistan Endocrine Society (PES) , Academic Director of the BMJ/AKU/RCP Post-graduate Diabetes certification course
Aga Khan Hospital, Karachi

Dr. Azra Rizwan
FCPS Medicine
Postgraduation Diabetes & Endocrinology Certification AKUH, MSc Clinical Research,
Aga Khan University Hospital, Karachi

Dr. Fatima Zahra
FCPS , MACE
Fellowship in Diabetes and Endocrinology (JPMC)
Endocrinologist Ruth Pfau Medical College
Executive member PES

Dr. Ibrar Ahmad
FCPS (Medicine), FCPS (Endocrinology), FRCP
Consultant Diabetologist & Endocrionologist
HOD Department of Diabetes & Endocrinology & Metabolic Disease
Lady Reading Hospital, Peshawar
President Pakistan Endocrine Society

Dr. Mujeeb Ur Rehman
MRCP, FCPS (Medicine), FCPS (Endocrinology)
Lady Reading Hospital, Peshawar

Dr. Musarrat Riaz
FCPS (Med), FCPS (Endo)
Baqai Medical University,
Karachi

Dr. Saima Askari
FCPS (MED), FCPS (ENDO)
Baqai institute of Diabetology and Endocrinology
Baqai Medical University, Karachi
Executive Member, Pakistan Endocrine Society

Dr. Saira Furqan
MRCP, FCPS (Medicine), FCPS (Endocrinology)
Aga Khan University Hospital, Karachi

Dr. Shehla Tabassum
FCPS (Medicine), FCPS (Endocrinology)
FACP (USA), FACE (USA), MRCP (UK)
FRCP (UK), MRCP (Ireland)
SCE UK (Diabetes & Endocrinology)
Farooq Hospital, Lahore

Dr. Shair Zaman Kakar
MBBS BMC Quetta
FCPS (Medicine), FCPS (Endocrinology)
Consultant Diabetologist & Endocrinologist
BMCH Quetta

Dr. Tahir Ghaffar
MRCP, FCPS (Medicine), FCPS (Endocrinology)
Hayatabad Medical Complex Peshawar

Dr. Usman Musharraf
FCPS (Medicine), FCPS (Endocrinology)
Allied Hospital, Faisalabad

Dr. Uneeba Syed
FCPS (Medicine), FCPS (Endocrinology), CRCP
Jinnah Hospital, Lahore

Dr. Uzma Malik
FCPS (Medicine), FCPS (Endocrinology), CMT, PHD Fellow
KEMU, Lahore

Dr. Naeem Durrani
FCPS (Medicine), FCPS (Endocrinology)
Acting Assistant Professor
Bolan Medical Complex Hospital, Quetta
Consultant Endocrinologist AKUH.

Dr. Waqas Shafiq
FRCP (Edin), MRCP Diabetes & Endocrinology (UK), CCT Diabetes,
Endocrinology & Internal Medicine (UK)
Consultant Endocrinologist / Hospitalist
Shaukat Khanum Memorial Cancer Hospital & Research Centre

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www.pakendosociety.org

THYROID BOOKLET REVIEWERS

Prof. Dr. A.H. Aamir
MRCP,FRCP,FACE, CCT (Internal Medicine & Endocrine)
Hayatabad medical complex Peshawar

Dr. S. Abbas Raza
MD(USA) FACP(USA) DABIM
Shaukat Khanum Memorial Cancer Hospital & Research Centre (Lahore)

Prof. Dr. Saeed A. Mahar
FCPS, FACP, FACE, FRCP(London)
National Institute Of Cardiovascular Diseases Karachi

Prof. Dr. Khurshid Ahmad Khan
MD, (USA), F.A.C.E (USA)
Diplomate of American Board in Diabetes & Endocrinology (USA)
Diplomate of American Board in Internal Medicine (USA)
Fatima Memorial Medical & Dental College, Lahore

Prof. Dr. Najmul Islam
MRCP,FRCP
Aga Khan University Hospital, Karachi

Dr. Sarah Nadeem
American Board (Internal Medicine & Endocrinology, Diabetes and Metabolism)
Aga Khan University Hospital, Karachi

Dr. Qamar Masood
MBBS; FACP; FACE; DABIM; Diplomate American Board in Endocrinology, Diabetes and Metabolism
Aga Khan University Hospital, Karachi

Dr. Sadia Salman
FCPS (medicine),FCPS(Endocrinology)
Allama Iqbal Medical college/Jinnah Hospital, Lahore

Dr. Osama Ishtiaq
MCPS, FCPS (2004), FACE (2013),
Fellowship in Diabetes and Endocrinology (AKUH)
Shifa International Hospital, Islamabad

Foreword

In recent years, the clinical evolution of thyroid diseases has been studied exhaustively as new discoveries have been made about thyroid malfunction and the effective management of patients. **Thyroid Diseases** present a comprehensive exposition of a range of disorders caused by thyroid dysfunction.

Thyroid hormones affect virtually all systems, and abnormal thyroid function may have protean manifestations. The first step is to decide whether the patient is hypothyroid or hyperthyroid based on clinical manifestations and the results of thyroid function tests. Treatment is then determined on the underlying cause, symptoms, and additional testing. Hypothyroidism and thyrotoxic states are most frequently encountered in the outpatient setting but in severe cases may require hospitalization

This comprehensive booklet is the first of its kind from Pakistan Endocrine Society for doctors about Endocrine topics and provides core understanding and clinical knowledge to all those involved in managing thyroid disorders. The authors have included the basic thyroid glandular functions which are essential in understanding the pathophysiology and clinical aspects of this disease.

Some special and important issues such as pregnancy and thyroid diseases, subclinical thyroid dysfunction, how to assess thyroid nodules and when to refer to surgeon are also included.

Dr. Abdul Jabbar
Founder Member and Former President
Pakistan Endocrine Society

Preface

Thyroid gland disorders are among the most common endocrine conditions evaluated and treated by clinicians. Patients with thyroid disease are seen in many different general and specialist clinics because of the varied modes of presentation. This thyroid booklet aims to highlight common presentations and clinical management of thyroid disorders specially for family physicians and those practicing at primary and secondary care level.

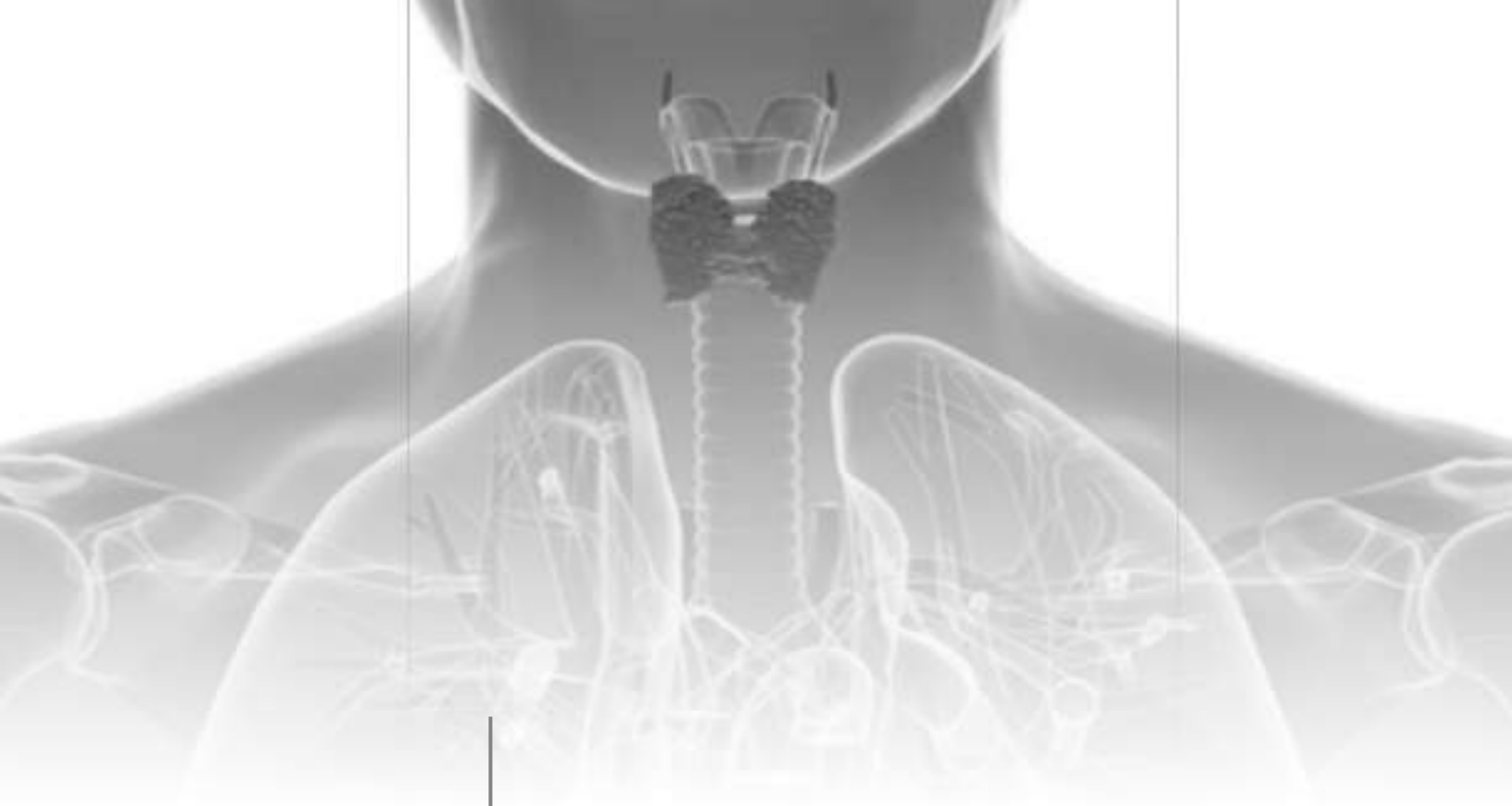
Although very comprehensive guidelines for evaluation and management of thyroid disorders are available internationally, it becomes difficult for busy clinicians to keep themselves updated. Inappropriate treatment on unconfirmed thyroid disorders is still encountered in clinical practice. Similarly, laboratory reports are often not correlated with clinical status before starting treatment for thyroid disorders. Coordinated management of thyroid disorders involves almost all the specialties of modern medicine.

Pakistan Endocrine Society as part of its academic initiatives has come up with this collection of articles related to various aspects of managing thyroid disorders like, thyroid nodule, interpretation of thyroid function tests (TFTs), hypo and hyperthyroidism, thyroid disorders during pregnancy, initiation and dose adjustments of thyroxine etc. specially targeting family physicians and other sub-Specialities. The material is presented in a simple to understand language mainly focusing on practical aspects to make it reader friendly.

The editorial team is very grateful to all the contributors for their valuable time and contribution and hope that this booklet will help clinicians in managing their patients in a better way.

Dr. Ibrar Ahmed
President
Pakistan Endocrine Society

Dr. Musarrat Riaz
Publication Secretary
Pakistan Endocrine Society



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Overview Of Thyroid Gland

Dr. Fatima Zehra
Dr. Usman Musharraf

Introduction

Thyroid disorders are very common and mainly tend to occur in females but can affect at any age and gender from neonates to elderly. In order to identify and manage thyroid disorders we need to know the physiology of thyroid hormones in addition to the feedback mechanism. A physician should be able to deal with common thyroid disorders and give appropriate and timely referrals to the endocrinologists.

Anatomy and location

Thyroid gland is an organ in neck resembling that of butterfly, consists of two lobes, left and right. Both the lobes are connected by a narrow band of tissue, called as "isthmus". The gland is larger in female than in male and its size further increases during pregnancy. Weight of this gland in adults is around 25 grams. Thyroid gland has tremendous potential for growth, enlarged thyroid is commonly termed as goiter; size of which can be hundreds of grams. (1)

A thin fibrous capsule covers the thyroid gland, which consists of two layers. Outer layer of capsule attaches thyroid gland with thyroid and cricoid cartilages as it is continuous with pretracheal fascia. It causes thyroid gland to move with swallowing. While inner layer of capsule extrudes into gland to form septa which further sub divide thyroid tissue into microscopic lobules. (2)

Right thyroid lobe has more vascular supply then left one and obviously larger then left lobe. Sometimes when thyroid gland is enlarged, a finger like projection can be felt upward and left lateral to midline, called as pyramidal lobe.

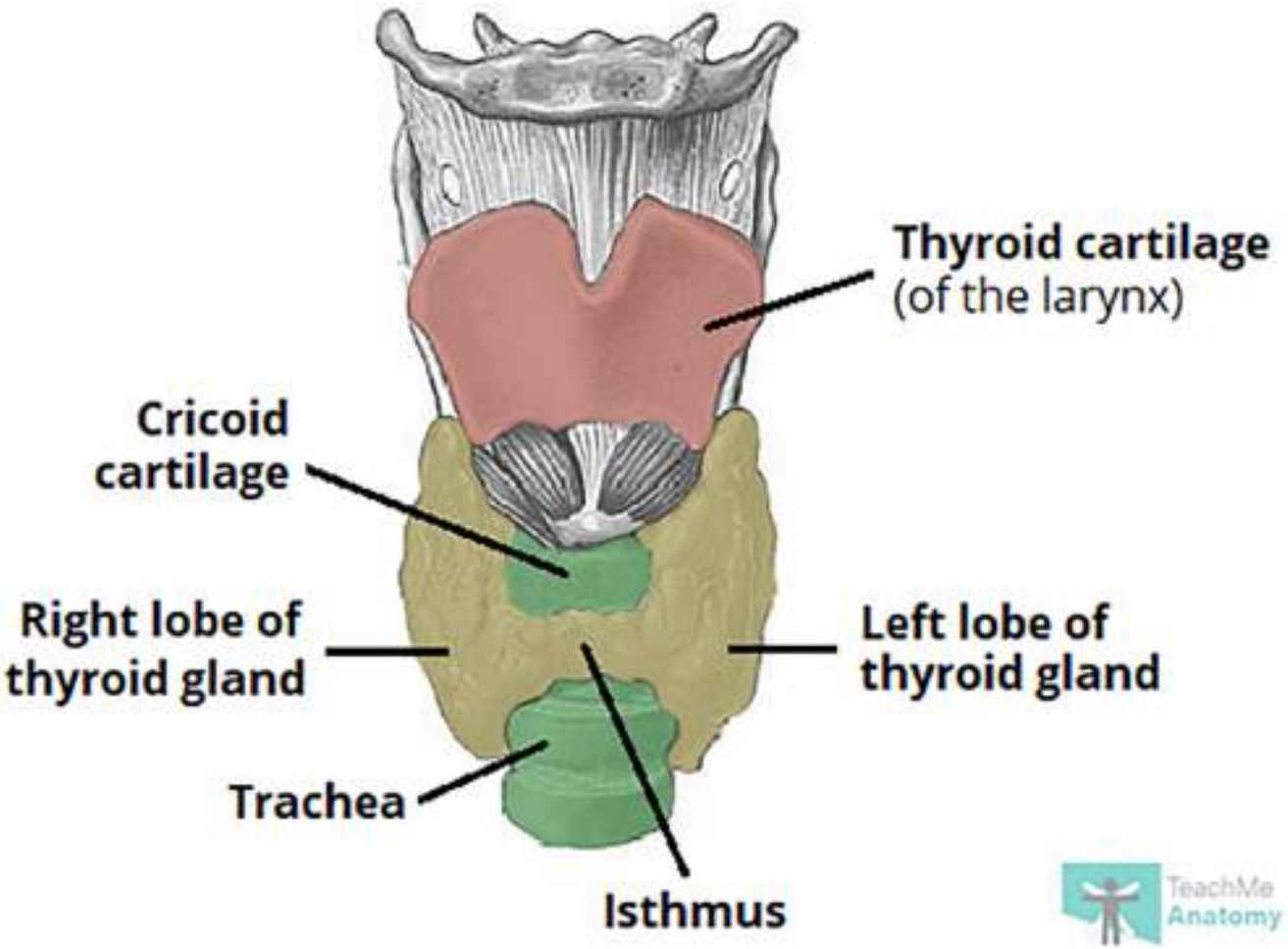
Blood flow in thyroid gland ranges from 4 to 6 ml/min/g, which is more than blood flow to kidneys. In graves' disease, flow may increase to 1 L/min/g and this much high flow is the reason of thyroid bruit.

Thyroid gland consists of packs of spherical units, termed as follicles having rich capillary network. These follicles are filled with clear proteinaceous fluid that constitutes major part of thyroid gland.

On cross section, thyroid tissue looks like a structure of closely packed ring that consists of a lumen surrounded by a single layer of cells. Average diameter of lumen is 200 nm but it varies considerably even within same thyroid gland and follicular cells are cuboidal in inactive phase while columnar in active phase of thyroid hormone secretion. 20 to 40 follicles form a lobule and different lobules are separated from each other by a layer of connective tissue and each lobule is supplied by single artery. Function of one lobule may be different from that other.

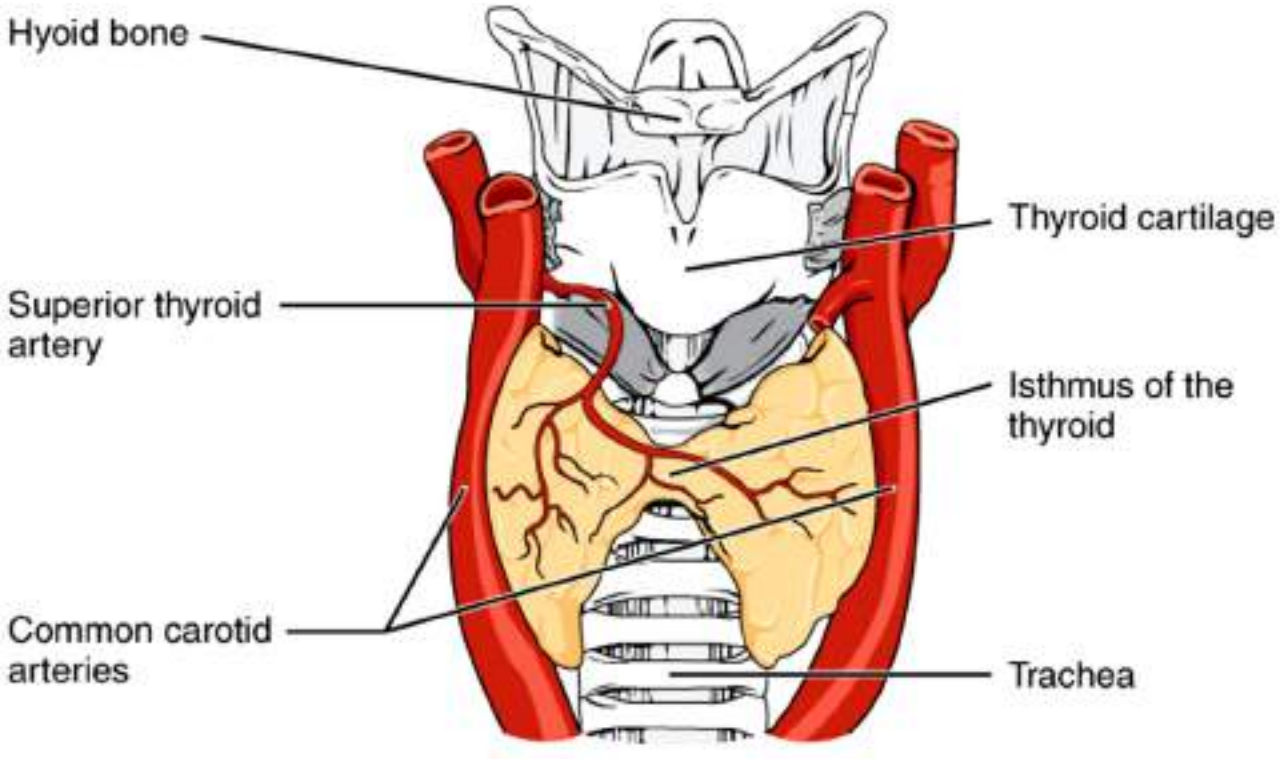
Thyroid gland also contains C cells of parafollicular cells, which are the source of Calcitonin. These cells migrate bilaterally from neural crest.

Thyroid gland lies in front of neck and in front of trachea and larynx. Ccricoid cartilage lie just above thyroid gland and below Adam's apple. The uppermost part of thyroid lobe extends in front of thyroid cartilage and the lowermost part extends in front of fourth to sixth tracheal rings, while isthmus lies in front of second to third tracheal rings. Sternocleidomastoid muscles lies to the side of gland while infrahyoid muscles are in front of it. (3)



Structural Anatomy of Thyroid Gland

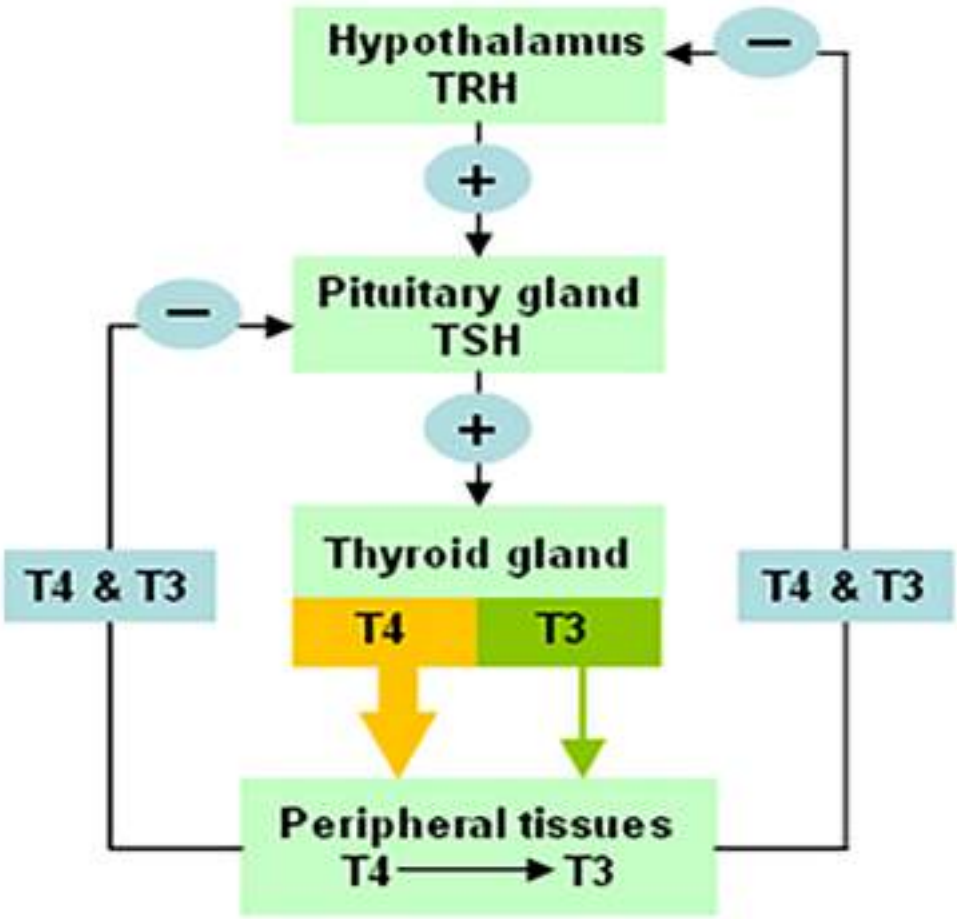
* Thyroid gland is supplied by superior and inferior thyroid arteries and sometimes by thyroid ima artery.
* Superior thyroid artery is a branch of the external carotid artery, inferior thyroid artery is a branch of thyrocervical trunk while thyroid ima artery has variable origin.
* Superior thyroid artery splits into anterior and posterior branches while inferior thyroid artery splits into superior and inferior branches.
* Venous blood is drained into internal jugular vein via superior and middle thyroid veins and into brachiocephalic veins through inferior thyroid veins.
* Lymphatic drainage is through pretracheal , paratracheal and prelaryngeal lymph nodes
* Thyroid gland receives its sympathetic nerve supply from the superior, middle and inferior cervical ganglion of the sympathetic trunk while parasympathetic nerve supply is from superior and recurrent laryngeal nerve. (1)



Blood Supply of Thyroid Gland

Hypothalamus-pituitary Axis (HPT)

Hypothalamus-pituitary-thyroid (HPT) axis control the thyroid gland at two levels for the secretion of thyroid hormones. firstly, Hypothalamic thyrotropin-releasing hormone (TRH) stimulates pituitary gland to release thyroid-stimulating hormone, (TSH), which in turn leads to the production and secretion of thyroid hormones (THs) by thyroid gland. The THs thyroxine (T4) and triiodothyronine (T3) control the secretion of TRH and TSH by negative feedback to maintain physiological levels of the main hormones of the HPT axis. (4) Reduction of circulating TH levels due to primary thyroid failure results in increased TRH and TSH production, whereas the opposite occurs when circulating THs are in excess. In plasma mostly thyroid hormones are bound to plasma proteins whereas metabolic state depends on free hormone rather than total hormone plasma concentration.



Reference: Hypothyroidism, Practice Essentials, Medscape (5)

Normal thyroid functions

The main function of thyroid gland is the production of iodine containing thyroid hormones triiodothyronine T3 and thyroxine T4. It mainly releases T4 thyroxine which is converted to T3 in peripheral tissues liver and kidney. Thyroid hormones are essential to regulate Basal metabolic rate to control vital body functions, including:

* Brain maturation
* Oxygenation of tissues
* Heart rate
* Breathing
* Body temperature
* Body weight
* Muscle strength
* Menstrual cycle
* Sexual function
* Sleep pattern

It also produces a peptide hormone calcitonin by parafollicular cells to maintain calcium homeostasis. (6)

Common thyroid problems

Euthyroid is the term used to describe the normal function of thyroid gland and characterized by levels of thyroid hormones within normal reference range.

Chapter 2

Interpretation Of Thyroid Function Tests Pearls Of Practice

Dr. Aisha Shaikh
Dr. Azra Rizwan

TSH is a hormone that is very sensitive to small changes in thyroid function. As thyroid function **slows down**, TSH **rises** through negative feedback signals from thyroid gland to pituitary gland. Initially, the rise in TSH is enough to stimulate a compensatory increase in Thyroid hormone (measured as Free T4). As, thyroid function progresses the TSH rise, even to phenomenally high levels is not adequate to maintain a normal thyroid function, leading to low **Free T4 levels**.

Hypothyroidism:

The most common causes of thyroid function slowing due to a poor functioning thyroid gland or Primary Hypothyroidism are:

* Iodine deficiency prevalent in the Northern areas of Pakistan where the soil is iodine deficient. This is because iodine is the essential substrate required for thyroid hormone synthesis.

* Hashimoto's Disease due to autoantibodies causing slowing of thyroid gland.

* Other causes include medication use such as lithium and amiodarone and congenital hypothyroidism.

Symptoms and signs of Primary Hypothyroidism include: body swelling, weight gain, disordered mentation/ poor concentration and/or memory, excessive fatigue, constipation, irregular menses, hoarseness of voice. Examination may reveal a diffuse goiter, very dry skin and delayed relaxation phase of ankle reflexes and non-pitting edema.

Case 1

A 25 year lady presents with menorrhagia and fatigue as well as body swelling and swelling around the eyes. Compete blood count reveals iron deficiency anemia, which alone could partly explain her symptoms. You also ask for a TSH. This is raised at **45 mIU/L.** You then ask for Free T4 and thyroid antibodies (no need for T4 and T3).

Free T4 is low at **0.5 ng/dl (0.76-1.8)** and Anti-TPO (thyroid peroxidase antibodies are **> 1000**).

Remember, the higher the TSH, **slower** thyroid function.

* She has Primary Hypothyroidism secondary to Hashimoto's disease.

* Management is straightforward with thyroxine replacement at 1.6ug/kg/day. So, in 60 kg lady, 96ug, approximately 100ug daily to be taken empty stomach ideally 45 minutes to 1 hour before breakfast (at least 30 minutes to breakfast).

* Advice to take any calcium, vitamin D, iron, multivitamin supplements at least 4 hours after thyroxine dose, so best taken at lunch and/or dinner. This is because of interactions of thyroxine with these medication as well as others such as Proton pump inhibitors (PPIs).

* In 6 to 8 weeks, we ask for a repeat TSH level. The aim is to keep TSH < 2.5 as she is a young lady in her reproductive age.

* The initial thyroxine dose may require up titration or down titration based on the TSH level.

Once the target TSH has been achieved, TSH monitoring can be done in 3 to 6 months' time, earlier if pregnancy is desired.

Case 2

A 35-year lady had testing for general fatigue. Her TSH is at **6.0.**
*Remember, the higher the TSH, **slower** thyroid function*
How would you proceed?

Important points of thyroid dysfunction in history and examination

Cold intolerance,	Weight gain,
Menstrual history (menorrhagia),	Decreased appetite,
Sleep pattern,	Difficulty in concentration,
History of miscarriage,	Family history of thyroid disease,
Difficulty in conceiving,	current pregnancy status
Planning to conceive	Goiter

In the indexed patient presence of a small goiter is noted. She is planning to conceive. In the past has had recent miscarriage although menses have generally been regular.

* **What is the likely diagnosis?**
  Subclinical hypothyroidism.
* **Would you like to order other tests?**
  Yes, Free T4 and thyroid antibodies.
* **How should you manage?**

In females of child bearing age, particularly having difficulty in conceiving, history of miscarriages, or currently pregnant, (symptoms such as fatigue are non-specific), it is best to replace thyroid hormones starting with low dose thyroxine 50ug to be taken empty stomach on daily basis.

Treat in these situations if TSH **more than or equal to upper limit of normal**, (check your local lab's reference ranges, generally the upper limit for TSH is 4.2 for most labs), irrespective of thyroid antibody positivity. So, even if thyroid antibodies were negative, treatment with thyroxine is advised with **target TSH goal of < 2.5** mIU/L. The need to continue thyroid hormone replacement later in life (once she completes her family) should be revisited and many women can go off thyroxine replacement.

In subclinical hypothyroidism, TSH raised, Free T4 normal.
Thyroid antibodies are positive in Hashimoto's disease even in earlier stages of disease.
Monitoring of treatment effect in both Primary Hypothyroidism and subclinical hypothyroidism is with TSH.

Case 3

A 50 year male, has 3 children all healthy presents with TSH of 7.3 mIU/L done a month back. Testing was done as a result of executive checkup. On history, he reports having had some lethargy over the previous months. No family history of thyroid disease.

On examination, no body swelling, no goiter.

How would you manage?

* *No need of thyroid hormone replacement.*
* *Repeat TSH and Free T4 with thyroid antibodies after 2-3 months, since there is no urgency of treatment.*

This TSH elevation could be the result of self-limiting viral flu causing thyroiditis, which may have gone unnoticed by patient. Firstly, there is a hyperthyroid, followed by euthyroid, then hypothyroid phase which is transient in majority of cases.

Case 4

A 24 year male presents with headache and reduced libido. Work up reveals a low fasting 8am testosterone of 90 ng/dl (300-1000). LH and FSH levels are also low, indicating hypogonadotropic hypogonadism, a central/hypothalamic-pituitary cause for the hypogonadism.

Other hormonal work up was sent to look for further hormonal deficiencies. This revealed a TSH of **2.9 mIU/L** (0.4-4.2) and **Free T4; 0.4** (0.89-1.76), 8am cortisol was 5ug/dl, also low.

As you can see, Free T4 is remarkably low. With this level of Free T4 the TSH is expected to rise phenomenally. However, if there is a central lesion impacting TSH producing cells or thyrotropes, this TSH rise would not be seen.

His MRI revealed a Pituitary macroadenoma. In addition to surgical intervention, he would require steroid, **thyroxine** and testosterone replacement (always replace steroid hormones first and then thyroid hormones when there is co-existent deficiency of both hormones otherwise an adrenal crisis can be precipitated).

How to monitor adequacy of thyroid hormone replacement in cases of secondary hypothyroidism, it is the **Free T4** level that is monitored for medication adjustment (as TSH will remain low/inappropriately normal irrespective of treatment). The aim is to keep Free T4 in upper quadrant of normal range.

Secondary hypothyroidism most commonly results from disease of the pituitary such as macroadenomas, suprasellar lesions, pituitary apoplexy and Sheehan's syndrome. In secondary hypothyroidism, Free T4 would invariably be low, TSH can be either low, in normal range or a little above normal range. This is defined as TSH being inappropriately normal, as in the presence of a low circulating thyroid hormone, TSH would be expected to rise several folds.

Primary Hyperthyroidism

Primary hyperthyroidism is due to excess thyroid hormone in the circulation. This excess level may result from increased production of thyroid hormone by the thyroid gland or increased release of thyroid hormone into the circulation. The most common causes for increased production are: Graves' disease due to stimulating autoantibodies, toxic adenoma and multinodular toxic goiter (MNG). Subacute thyroiditis is the most common cause for increased **release** of thyroid hormone.

What will the Thyroid function tests look like in primary hyperthyroidism?
In most cases of primary hyperthyroidism, both **Free T4 and T3** levels are **increased**, and through negative feedback, **TSH is suppressed** (low).

Important points of thyroid dysfunction in history and examination

Heat Intolerance/ Hyperthermia	Weight Loss,
Excessive Sweating	Increased Appetite,
Palpitations	Abnormal Heartbeat
Diarrhea	Abdominal Pain
Tremulous Hands	Irritability,
Nervousness	Insomnia
Family History Of Thyroid Disease,	Tachycardia
Tachycardia	Warm, Sweaty Palms
Fine Tremors	Lid Retraction/lid Lag
Goiter	Thyroid Eye Disease

Most common cause of hyperthyroidism in a young female with diffuse goiter would be Graves' Disease. Patients with Graves' Disease may also have typical features of ophthalmopathy- eye signs such as proptosis, exophthalmos -and dermopathy.

How to determine the cause of hyperthyroidism:

Remember the three most common causes of hyperthyroidism are:

* Graves' Disease (GD)
* Toxic adenoma (TA)
* Toxic multinodular goiter (Toxic MNG)

It is important to identify the exact cause of hyperthyroidism in your patient since the choice of therapy, prognosis and whether the disease can go in to natural remission is based upon the exact etiology of the condition.

TSH receptor antibodies (TRAB):

In patients with hyperthyroidism with a diffuse goiter or no goiter, the test of choice would be TSH receptor antibodies (TRAB) levels which are positive in more than 90% patients of Graves' Disease, with high specificity.

Nuclear uptake scans {Tc-99 m pertechnetate thyroid scan or radioactive iodine (I-123 uptake scan)

In case of solitary (single) nodule enlargement or multinodular goiter (MNG), to test for functionality, thyroid scan is recommended.

* Scans of toxic MNG would reveal increased patchy uptake by the nodules.

* Scans of TA or solitary nodule would reveal increase uptake in that single nodule.

* In comparison, there is diffuse uptake in Graves' Disease.

* In case of subacute thyroiditis, uptake on thyroid scan would be negligible.

Treating hyperthyroidism:

* Treatment of hyperfunctioning gland (GD, TA, Toxic MNG) includes initiating anti-thyroid medication like carbimazole (thyroid peroxidase inhibitors), which inhibit production of the thyroid hormone at a dose of 10-40mg/day, depending on severity of hyperthyroidism and size of gland.

* Symptomatic treatment includes beta blockers like propranolol at dose of 20-40mg twice or three times daily. These agents inhibit the enhanced sympathetic activity such as palpitations, hand tremors.

Monitoring treatment:

* To monitor effect of treatment, in addition to **clinical response** in terms of weight regain, resolution of palpitations, abdominal pain, **biochemical response** is through **free T4** (T3 in case of T3 toxicosis) measurement.

* TSH can remain suppressed for months after attainment of clinical response and normalization of thyroid hormone levels and thus is not an ideal test to monitor response or treatment adjustment in initial few months of treatment.

Tapering off carbimazole in GD

* Once Free T4 is in normal range, the carbimazole dose can be slowly tapered down on 2 to 3 monthly basis, so as to maintain euthyroidism.

* GDpatients may remain in remission off carbimazole therapy, after a 12 to 18-month course. In case of recurrence, these subjects can be offered long term low dose treatment with these anti-thyroid medications.

When to consider definitive treatment (RAI or surgery)

* If the patient desires, definitive treatment with Radioactive Iodine (RAI) treatment can be offered to these subjects. RAI can also be used in cases where high doses of anti-thyroid agents fail to achieve euthyroidism.

* Most patients with large toxic MNGs and Ta would require definitive therapy with RAI or surgery following initial stabilization of thyroid levels with anti-thyroid medication.

Subacute thyroiditis:

Subacute thyroiditis (SAT) typically presents with neck pain, preceded by a viral flu. Neck tenderness may be apparent. The Erythrocyte Sedimentation Rate (ESR) is invariably raised in cases of subacute thyroiditis. At times, symptoms may be subtle in which cases thyroid scan would reveal the diagnosis with negligible uptake.

Managing SAT:

* In cases of SAT, symptomatic relief with Non-steroidal anti-inflammatory medication and propranolol is recommended.
* If neck pain relief is not achieved, a course of steroids (typically prednisolone 10-30 mg daily) over 6-8 weeks followed by tapering-off of steroids is recommended.
* The TSH & FT4 should be monitored 6-8 weekly for next few months to observe the hypothyroid phase and possible return to the euthyroid status.

Remember Anti thyroid drugs are **not** recommended in SAT as there is increased release of preformed thyroid hormone in this scenario, not increased formation.

Case 5

A 24 year lady, single, presents with weight loss, palpitations, tremulous hands for previous 3 months. On examination, pulse rate is 120 beats/minute, regular. She has warm sweaty palms and fine tremors of outstretched hands. On examination, there is a small diffuse goiter, non-tender and a faint bruit. There are no eye signs of ophthalmopathy or skin signs. Blood tests reveal a **TSH < 0.05**, **Free T4 3.6** (0.8-1.76).

In a young lady with primary hyperthyroidism, Graves' hyperthyroidism is the likely diagnosis. This can be confirmed with measurement of TRAB levels, which are invariably elevated in GD. Treatment would consist of anti-thyroid medication with carbimazole 30mg/day in two to three divided doses. Symptomatic treatment with propranolol 40-80mg/day would help to address the tremors and palpitations. ***The patient should have a Free T4 re-checked after 6 -8 weeks-TSH is likely to remain suppressed for a few months so it is important to adjust treatment based on Free T4 levels.***

Case 6

A 60-year lady presents with a large neck swelling, weight loss. On examination, there is a multinodular goiter. There is no retrosternal extension and no compressive symptoms. TSH is suppressed, < 0.05 and free T4 elevated at 3.0. The next step would be to ask for a Thyroid Scan, to assess the functionality. This reveals patches of **increased uptake** in the nodules. The diagnosis is toxic MNG. This patient would benefit from RAI treatment as definitive treatment. In the meantime, she should be rendered euthyroid with use of carbimazole and beta blockers prior to radioiodine treatment. Untreated hyperthyroidism can lead to atrial fibrillation and osteoporosis. Thyroid storm can be precipitated during RAI treatment.

Case 7

A 40 - year male presents with lethargy. A general practitioner asked for thyroid function tests and thyroid antibodies. The TSH and Free T4 are within the normal range. The thyroid antibodies are elevated. The patient would like to know whether low dose thyroid hormones would be helpful.

Since the thyroid functions are normal, there is no evidence to suggest benefit from thyroxine treatment. TSH level should, however be periodically checked after 6 to 12 months to ensure that a decline in thyroid function does not occur over time, the risk of which is expected to be high owing to underlying thyroid autoimmunity.

Case 8

A young primigravida presents at 11th week gestation with thyroid function test results that her gynecologist had asked her to do for intermittent palpitations. Her TSH is suppressed at 0.01 mIU/L, T4 is 15.5 mcg/dl (5-11), Free T4 is 1.7 ng/dl (0.89-1.76).

Palpitations are a non-specific symptom that can occur in pregnancy due to cardiovascular alterations. TSH suppression in the first trimester of pregnancy is a common occurrence due to the structural homology of TSH molecule with the HCG molecule, the latter being produced in high quantities by the placenta. Since most laboratories do not report trimester specific levels of Free T4, we rely more upon T4 levels during pregnancy. In addition, the upper limit of normal for total T4 in pregnancy is actually 17.5 (not 11 as in non-pregnant state)- that is 1.5 times upper limit of normal of non-pregnant state. Hence, in this case we will not be treating with anti-thyroid medication. The patient needs to be reassured accordingly.

Other thyroid and pregnancy related problems require referral to the Endocrinologist.

Chapter 3

Hypothyroidism

Dr. Uzma Jahanzeb
Dr. Shehla Tabassum

Hypothyroidism is the most common thyroid disease that leads to under functioning of thyroid gland and characterized by low levels of thyroid hormones (T3 and T4)

* If Free T4 is low with high TSH it means thyroid gland is affected and patient has primary hypothyroidism.
* However, if Free T4 level is below normal range and low TSH level is also seen then patient has secondary hypothyroidism.

Causes of primary Hypothyroidism (7)

1. Hashimoto's thyroiditis (autoimmune condition anti-TPO antibodies positive)
2. Iodine deficiency
3. Radioactive iodine therapy
4. Surgery of thyroid (subtotal/total thyroidectomy)
5. Drugs -lithium, amiodarone, interferon
6. Subacute thyroiditis (transient)

CASE SCENARIO

A 32-year-old woman presents in the OPD with complaints of progressive weight gain and generalized body aches from the last 2 years. She is married for 3 years, is trying to conceive but has not been successful. There is no history of increased body hair growth, menstrual irregularity, acne or proximal myopathy. She is not a diagnosed case of Diabetes, hypertension or dyslipidemia. Physical examination is unremarkable. Baseline CBC, LFTs and RFTs turn out to be normal. Thyroid function tests (TSH and FT4) were ordered. The results showed TSH of 43 (0.4-4), Free T4 is low at **0.5 (0.76-1.8)** and Anti-TPO (thyroid peroxidase antibodies are **> 1000**).

How will you proceed further?

Key points

* Correct identification of symptoms of hypothyroidism
* Proper evaluation of hypothyroidism
* Appropriate management of hypothyroidism
* Approach in a patient with subclinical hypothyroidism

Introduction

Deficiency of thyroid hormones production leads to the development of Clinical entity of "Hypothyroidism". Decreased levels of T4 and T3 in the blood leads to compensatory increase in TSH secretion. This condition has got detrimental effects on multiple organ systems and is a big cause of morbidity all over the world. Pakistan is one of moderately iodine-deficient countries in the world. Consequently, hypothyroidism is found to be prevalent in 4.1% of its population[1]. Hypothyroidism is 5-8 times more common in women than men. Majority of hypothyroid patients have a goiter.

Main types

1. Primary Hypothyroidism: results from primary thyroid disease
2. Secondary Hypothyroidism: results from hypothalamic-pituitary disease

Etiology

PRIMARY HYPOTHYROIDISM
1. Autoimmune Hashimoto's thyroiditis
2. Radioactive iodine therapy for Grave's Disease
3. Total or Subtotal thyroidectomy
4. Excessive iodine intake (kelp, radiocontrast dyes)
5. Subacute thyroiditis (usually transient)
6. Iodine deficiency
7. Inborn errors of thyroid hormone synthesis
8. Drugs (lithium, interferon-alfa, amiodarone)
SECONDARY HYPOTHYROIDISM
1. Pituitary adenoma
2. Pituitary ablative therapy (irradiation)
TERTIARY HYPOTHYROIDISM
1. Hypothalamic dysfunction (rare)

Table 1. Adapted from David S. Cooper, Paul W. Ladenson. Greenspan's basic & Clinical Endocrinology. 10th edition. United States of America:Lange;2018. Chapter 7;Thyroid gland;p.200

Common Presenting Symptoms

* Fatigue, loss of energy, lethargy
* Weight gain
* Decreased appetite
* Dry skin
* Hair loss
* Sleepiness
* Cold intolerance
* Muscle pain, joint pain
* Depression
* Emotional liability, mental impairment
* Forgetfulness, impaired memory, inability to concentrate
* Constipation
* Menstrual disturbances, impaired fertility

Common Physical Signs

* Weight gain
* Slowed speech and movements
* Dry skin
* Coarse, brittle hair
* Dull & coarse facial features
* Periorbital puffiness
* Goitre (diffuse or nodular)
* Hoarseness
* Decreased systolic blood pressure and increased diastolic blood pressure
* Bradycardia
* Non-pitting edema (myxedema)
* Delayed relaxation of deep tendon reflexes

DIFFERENTIAL DIAGNOSIS OF HYPOTHYROIDISM

* Polycystic Ovarian Syndrome
* Iron deficiency Anemia
* Obstructive Sleep Apnea
* Depression
* Cushing Syndrome
* Chronic fatigue Syndrome

DIAGNOSTIC TESTS

1. THYROID FUNCTION TESTS (TFTs)

* TSH
* Free T4 (preferred) or Total T4
* In primary Hypothyroidism, TSH will be elevated and Free T4 will be suppressed
* In secondary/central hypothyroidism, TSH will be normal or only slightly elevated and even suppressed but Free T4 will also be suppressed
* TSH is the best screening test for primary hypothyroidism[2]
* Free T4 is the best screening test for secondary/central hypothyroidism

2. THYROID AUTOANTIBODIES

* Anti-TPO (thyroid peroxidase) Antibodies
* Elevated in 95% cases of Hashimoto's thyroiditis[3]

3. COMPLETE BLOOD COUNT (CBC)

* Macrocytic anemia
* Microcytic anemia due to menorrhagia

4. OTHER BIOCHEMICAL ABNORMALITIES

* Hyponatremia
* Slight elevation in Prolactin levels
* Raised Creatinine Kinase (CK)
* Increased LDL Cholesterol

5. ULTRASOUND THYROID

* **NOT INDICATED** unless a thyroid nodule or Multinodular goiter is palpable

MANAGEMENT

* **Levothyroxine**
  - > Initiate treatment when TSH is at least greater than 10
  - > Usual Dose in Adults: 1.6-1.8 µg/kg body weight[4.]
  - > Levothyroxine should be started with low doses (25µg/day) in older patients (over 65 years) and heart disease patients. Dose should be titrated slowly on weekly basis to reach the optimal weight-based calculated dose
  - > Weight-based dose in Children:
    - · 1-3 years of age: 4-6mcg/kg body weight
    - · 3-10 years of age: 3-5mcg/kg body weight
    - · 10-16 years of age: 2-4mcg/kg body weight
    - · Thyroxine is ingested in the fasting state (usually 1 hour before breakfast)
  - > Iron and Calcium hamper the absorption of Thyroxine so there must be a gap of at least 4 hours between the intake of Thyroxine and Iron/Calcium supplements
  - > Levothyroxine has a long half-life of 7 days so this feature enables the patient to take two doses at once if a dose is missed/omitted
  - > Dose adjustments should be made with "TSH" assessment 6-8 weeks after any dosage change in cases of primary hypothyroidism
  - > Dose adjustments should be made with "Free T4" assessment 6-8 weeks after any dosage change in cases of secondary/central hypothyroidism
  - > Dose adjustment is specifically indicated in cases of large changes in body weight, with aging and during pregnancy
  - > There is no role for the use of levothyroxine in treating Euthyroid patients with depression, obesity or urticaria[5]
  - > Addition of liothyronine to levothyroxine in hypothyroid patients is generally not recommended

Subclinical Hypothyroidism

* Defined as "high serum TSH level in the presence of normal serum Free T3 and T4 levels"
* These patients are usually asymptomatic or may have very few non-specific vague symptoms of hypothyroidism
* Prevalence is higher in women than men
* It is usually diagnosed by incidental laboratory finding of raised TSH and normal Free T4 level
* Annual measurement of TSH is advised in patients with subclinical hypothyroidism
* Treatment for Subclinical hypothyroidism is generally not recommended
* Treatment with Thyroxine is usually indicated only when TSH rises above 10mU/L
* Treatment with low-dose Thyroxine may be indicated in:
  - > Infertile women with subclinical hypothyroidism and elevated Anti-TPO Antibodies level
  - > Pregnant women with previous history of miscarriages having subclinical hypothyroidism and elevated Anti-TPO Antibodies level

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Chapter 4

Hyperthyroidism

Dr. Saira Furqan
Dr. Naeem Durrani

* Hyperthyroidism is characterized by increased thyroid hormone synthesis and secretion from the thyroid gland.
* Thyrotoxicosis refers to the clinical syndrome of excess circulating thyroid hormones, irrespective of the source.
* The most common cause of hyperthyroidism is Graves' disease, followed by toxic nodular goiter.
* Treatment options for Graves' disease include antithyroid drugs, radioactive iodine therapy, and surgery,
* â blockers are used in symptomatic thyrotoxicosis, and might be the only treatment needed for thyrotoxicosis not caused by excessive production and release of the thyroid hormones.
* Thyroid storm and hyperthyroidism in pregnancy and during the post-partum period are special circumstances that need careful assessment and treatment.

Case: A 35 years old female presented to emergency department for evaluation of progressive sub-sternal chest discomfort over the preceding 5 days. She had a 2 weeks history of palpitations, shortness of breath and unintentional weight loss followed by a febrile illness and sore throat. On examination her pulse is 122 beats per minute and BP is 140/90. She has no goiter but have fine tremors of outstretched hands, her skin is warm and moist and she has hyperreflexia. ECG showed sinus tachycardia and Thyroid function tests are TSH: <0.005 u IU/ml (0.4-4.2) with FT4 level of 2.6 ng/dl (0.89-1.72).

The most appropriate next investigation is:

A: Ultrasound Neck
B: Serum Thyroglobulin level
C: Tc 99 Thyroid scan
D: Fine needle aspiration cytology
E: CRP level

Introduction

Hyperthyroidism is a pathological disorder in which excess thyroid hormone is synthesised and secreted by the thyroid gland. The terms thyrotoxicosis and hyperthyroidism are usually used interchangeably but there is a difference between both of them.

"Thyrotoxicosis" refers to a clinical state that results from inappropriately high thyroid hormone action in tissues due to inappropriately high tissue thyroid hormone levels.

This elevation of thyroid hormones may be because of increase production from the thyroid gland itself, exogenous administration of thyroid hormones or because of release of excessive amount of thyroid hormones due to gland destruction as in thyroiditis.

Hyperthyroidism is a form of thyrotoxicosis due to inappropriately high synthesis and secretion of thyroid hormone(s) by the thyroid gland and it is no longer under regulatory control of hypothalamic-pituitary centers, characterized by a hypermetabolic state.

Thyroiditis is the inflammation of thyroid gland associated with excessive release of preformed thyroid hormone in the blood. The diagnosis of subacute thyroiditis is based on clinical history, physical examination, laboratory data (In addition to suppress TSH and FT4 there will be increase ESR or CRP level in thyroiditis), and Radioactive Iodine Uptake scan (Low uptake on Tc99 Scan). Subacute thyroiditis presents with moderate-to-severe pain in neck, often radiating to the ears, jaw, or throat. Patients may have a prodrome of malaise, low-grade fever, pharyngitis symptoms, and fatigue. The thyroid gland may be slightly enlarged and is firm and painful to palpation.
For appropriate treatment, accurate diagnosis is required as treatment for each condition is different.

Symptoms (Common only)

* Weight loss despite of increase appetite
* Increase frequency of defecation/ Diarrhea
* Hand tremors
* Heat intolerance
* Palpitations
* Exertional shortness of breath
* In female, menstrual irregularities
* Anxiety, restlessness, sleeplessness
* In case of Graves' disease eye symptoms like proptosis, lid retraction lid lag etc.
* In case of thyroiditis, history of fever, neck pain and difficulty in swallowing

Signs (Common only):

* Tachycardia
* Hand tremors
* Hyperreflexia
* Proximal Myopathy
* Eye signs and diffuse goitre in case of Graves' disease
* Tenderness of thyroid gland in case of Thyroiditis
* Palpable Nodule or multinodular thyroid gland in case of toxic nodule and toxic multinodular goiter

Differential Diagnosis

TABLE 3. CAUSES OF THYROTOXICOSIS

Thyrotoxicosis associated with a normal or elevated radioiodine uptake over the neck[a]
GD
TA or TMNG
Trophoblastic disease
TSH-producing pituitary adenomas
Resistance to thvroid hormone (T3 receptor mutation)[b]
Thyrotoxicosis associated with a near-absent radioiodine uptake over the neck
Painless (silent) thyroiditis
Amiodarone-induced thyroiditis
Subacute (granulomatous, de Quervain's) thyroiditis
Iatrogenic thyrotoxicosis
Factitious ingestion of thyroid hormone
Struma ovarii
Acute thyroiditis
Extensive metastases from follicular thyroid cancer

Diagnostic tests:
Serum TSH and FT4 levels.

In Thyrotoxicosis TSH level is suppressed and FT4 level will be increased.

If TSH is suppressed and FT4 is normal, check Total T3 level because In milder hyperthyroidism, serum total T4 (TT4) and free T4 (FT4) can be normal, only serum total T3 (TT3) may be elevated, and serum TSH will be <0.01mU/L (or undetectable), this condition is called "T3-toxicosis"

If suspecting thyroiditis as a cause of thyrotoxicosis, take history of fever, neck pain or odynophagia. If these symptoms are present, check ESR level also in addition to TSH and FT4 levels. Definitive test to differentiate between thyroiditis and hyperthyroidism is Tc99 Thyroid scan. If it show diffuse increase in uptake it is Graves' disease and if it shows diffuse decrease in uptake, it is thyroiditis. (Remember thyroid scan in contraindicated in pregnant and lactating females). In cases where thyroid scan is not possible get TRAB level (Thyrotropin receptor antibody level). It will be negative in cases of thyroiditis whereas positive in Graves' disease.

In cases where on thyroid examination a nodule or multiple nodules present, Tc99 is advised to differentiate between Graves' disease and Toxic nodule or toxic multinodular goiter because the treatment of Graves ' disease and Toxic nodule/ toxic multinodular goiter is different.

Again if unable to get thyroid scan, TRAB levels can be checked. It is positive in Graves' disease whereas negative in cases of Toxic nodule or toxic multinodular goiter and thyroiditis.

Management:

Symptomatic control

Beta-adrenergic blockade should be considered in elderly asymptomatic and all symptomatic patients especially in

* Elderly symptomatic patients
* Patients with resting heart rates in excess of 90 bpm
* Coexistent cardiovascular disease

Start with Propranolol 10-40 mg q6-8h
Start with low dose and increase progressively until symptoms are controlled
In most cases dose of 80-160 mg/day is sufficient
Calcium Channel Blockers (Verapamil/ Diltiazem) can be used if beta blocker not tolerated or contraindicated (eg in patients with asthma, peripheral vascular disease)

Management of Graves' disease

Methimazole (Neomercazole) should be used in virtually every patient for Graves' disease, except

* First trimester of pregnancy
* Treatment of thyroid storm
* Patients with minor reactions to methimazole who refuse radioactive iodine therapy or surgery

In Above-mentioned conditions, instead of neomercazole, propylthiouracil can be used. Use of propylthiouracil is now very limited because of serious side effects particularly fulminant hepatic failure.
Prior to initiating antithyroid drug therapy for Graves ' disease a baseline complete blood count, including white count with differential, and a liver profile is recommended.
Start Neomercazole with a dose of 15-30 mg/ day. Can increase up to 60 mg/day but do remember with higher doses the chances of side effects increases.

A rough guide for initial dose of Neomercazole is as follow:

Daily dosing: 510 mg if free T4 is 11.5 times the upper limit of normal.
Daily dosing: 1020 mg for free T4 1.52 times the upper limit of normal.
Daily dosing: 3040 mg for free T4 23 times the upper limit of normal.
In cases where using propylthiouracil, start from 50150 mg three times daily according to the severity of hyperthyroidism.

An assessment of serum FT4 should be obtained about 4 weeks after initiation of therapy, and the dose of medication adjusted accordingly.

Serum TSH may remain suppressed for several months after starting therapy and is therefore not a good parameter to monitor therapy early in the course of the disease but later on TSH and FT4 both are advised to assess the disease status.

Appropriate monitoring intervals are every 48 weeks until euthyroid levels are achieved with the minimal dose of medication.

Once the patient is euthyroid, biochemical testing and clinical evaluation can be undertaken at intervals of 23 months.

A differential white blood cell count should be obtained during febrile illness and at the onset of pharyngitis in all patients taking antithyroid medication to assess for agranulocytosis. Patient should be informed before starting anti-thyroid drug, to stop taking anti-thyroid drug if experience fever with sore throat and consult doctor immediately. Ideally a written pamphlet of side effects of medicine should be given.

Routine monitoring of white blood counts is not recommended.

Liver function and hepatocellular integrity should be assessed in patients taking propylthiouracil who experience pruritic rash, jaundice, light-colored stool or dark urine, joint pain, abdominal pain or bloating, anorexia, nausea, or fatigue.

Anti-thyroid treatment should be continued for approximately 1218 months. With anti-thyroid drug, thyroid function tests starts improving. Once TSH and FT4 improves, start tapering the dose of anti-thyroid drug. At each visit adjust the dose according to TSH and FT4. Once TSH and FT4 remains within normal limits with minimal dose of drug, anti-thyroid drug can be discontinued but keep on monitoring the thyroid function tests as there are chances of disease relapse.

Side effects of Antithyroid drugs

Minor allergic reactions including pruritus
Major allergic/toxic events such as agranulocytosis, vasculitis, or hepatic damage. (Patient will present with symptoms as mentioned above like fever and sore throat, skin rash, abdominal pain, vomiting, jaundice etc)

Contraindications for anti-thyroid drugs
Known major adverse reactions to ATDs

Indications for Radio Active Iodine treatment:

* **Patients with hyperthyroidism**
* Patients' intolerant to anti thyroid medication
* Relapse of Graves' disease

Contraindications to Radio Active Iodine treatment

* Pregnancy
* Lactation
* Coexisting thyroid cancer
* Individuals unable to comply with radiation safety guidelines
* Females planning a pregnancy within 46 months

Indications for surgery

* Symptomatic compression or large goiters
* Suspected Thyroid malignancy
* Large nonfunctioning or hypo functioning nodule (Cold nodule on Tc99 thyroid scan)
* Patients with moderate to severe active Graves's ophthalmopathy (not controlled on antithyroid medications)
* Coexisting hyperparathyroidism

Contraindications for surgery

Cardiopulmonary disease
End-stage cancer
Other debilitating disorders

Management of Toxic Multinodular Goitre or Toxic Adenoma

Radioctive iodine ablation is the definitive treatment.

Thyroidectomy is indicated in cases of large goiter with compressive symptoms (like difficulty in breathing particularly in lying position, difficulty in swallowing and choking)

Before radioactive iodine ablation or surgery, control symptoms of hyperthyroidism with beta-blockers and antithyroid drugs. Can proceed for RAI/Surgery once TSH and FT4 levels normalizes on anti-thyroid treatment.

After radioactive iodine ablation keep monitoring TSH and FT4 levels (after every 6-12 weeks) because of chances of post ablative hypothyroidism. If patient develop hypothyroidism after radioactive iodine treatment, treatment with Thyroxine is indicated.

In patients who underwent total thyroidectomy, post-surgery thyroxine replacement is indicated.

Management of Thyroiditis:

Patients with mild symptomatic subacute thyroiditis should be treated initially with â-adrenergic-blocking drugs and nonsteroidal anti-inflammatory agents (NSAIDs).

Start with Propranolol 10-40 mg q6-8h. Start with low dose and increase progressively until symptoms are controlled. In most cases 80-160 mg/day is sufficient. Calcium Channel Blockers can be used if beta blocker are not tolerated or contraindicated.

In NSAIDs, commonly used agents are ibuprofen (800-1200 mg/day in divided doses) and naproxen (1-1.5 g/day in divided doses).

Corticosteroids should be used instead of NSAIDs when patients fail to respond (showing no improvement in clinical symptoms i.e fever, neck pain and difficulty in swallowing despite of adequate dose) or present initially with moderate to severe pain and/or thyrotoxic symptoms.

Standard recommendations are to use prednisolone 40 mg daily for 12 weeks followed by a gradual taper over 24 weeks or longer, depending upon clinical response i.e improvement in fever, neck pain and difficulty in swallowing.

Thyroid function tests should be done periodically (after 2-3 months) because thyroiditis is associated with a triphasic phase. Initially transient thyroxicosis (lasts in 3-6 weeks) then hypothyroid (can last up to 6 months) and then recovery phase. This hypothyroid phase may be transient or permanent. If patient remain hypothyroid then thyroxine replacement can be started.

Sub clinical Hyperthyroidism:

Subclinical hyperthyroidism is defined as a normal serum-free T4 (FT4) and normal total T3 (TT3) or free T3 (FT3), with subnormal serum TSH level.

When to treat Sub clinical Hyperthyroidism

Subclinical Hyperthyroidism: Treatment Strategies[a]

Factor	TSH (<0.1 mIU/L)	TSH (0.1-0.5 mIU/L)[b]
Age >65 years	Treat	Consider treating
Age <65 years with comorbidities		
Heart disease	Treat	Consider treating
Osteoporosis	Treat	Observe
Menopausal	Consider treating	Consider treating
Hyperthyroid symptoms	Treat	Consider treating
Age <65 years with comorbidities	Consider treating	Observe

Abbreviation: TSH, thyrotropin.

[a] Adapted from Bahn RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Endocr Pract. 2011:17:456-520 (reference 55).

[B] Where 0.5 mIU/L is the lower limit of the reference range.

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2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism And Other Causes of Thyrotoxicosis

Chapter 5

Thyroid Nodule

Dr. Waqas Shafiq
Dr. Uneeba Syed

Thyroid nodules are common in adults. The prevalence of palpable thyroid nodules to be approximately 5% in women and 1% in men living in iodine-sufficient parts of the world (1, 2). Studies using ultrasonography have estimated the prevalence of thyroid nodules to be 20 to 76% in the adult population (3). The clinical importance of thyroid nodules rests with the need to exclude thyroid cancer. The incidence of malignancy among nodules is approximately 5% (4) . However, there are studies which have suggested that it may be as high as 15% (5) . The incidence of thyroid cancer has increased dramatically during the past three decades and it is now the fastest growing cancer in women. Almost all of this increase is in papillary thyroid cancer. The reason for this is unclear, although many point to the increase in imaging studies of the neck where small thyroid nodules are discovered before they become apparent on physical exam.

Evaluation of Thyroid nodule:

History and Physical Examination:

A complete history and physical examination focusing on the thyroid gland and adjacent cervical lymph nodes should be performed. Following point in history should be emphasized:

1. Age and gender
2. History of head and neck irradiation
3. Rate of neck mass growth
4. Anterior neck pain
5. Hoarseness of voice, Dysphonia, dysphagia or dyspnoea
6. Symptoms of hyperthyroidism or hypothyroidism
7. Use of iodine containing drugs or supplements
8. Personal or family history of thyroid disease or cancer.

PHYSICAL EXAMINATION:

A careful examination focusing on the thyroid are cervical lymphadenopathy should be performed emphasizing the following:

* Thyroid size and consistency
* Location, consistency, size and number of nodules
* Condition of the overlying skin
* Nodules fixation to the surrounding tissue
* Neck tenderness and pain
* Cervical lymphadenopathy

* Pertinent historical factors predicting malignancy include
* History of childhood head and neck radiation therapy,
* total body radiation for bone marrow transplantation (42),
* familial thyroid carcinoma, or thyroid cancer syndrome (eg : MEN 2, a risk for medullary thyroid cancer) in a first degree relative,
* rapid nodule growth, and/or
* hoarseness.

Pertinent physical findings suggesting possible malignancy include

* vocal cord paralysis,
* cervical lymphadenopathy, and
* fixation of the nodule to surrounding tissue.

TSH level:

Serum thyrotropin (TSH) should be measured during the initial evaluation of a patient with a thyroid nodule.

TSH normal --- Ultrasound thyroid
TSH elevated --- Ultrasound thyroid and check Free T4
TSH low --- Check Free T4 and Free T3 and Thyroid scan should be obtained

a. Hot that is tracer uptake is greater than the surrounding normal thyroid- Hyperfunctioning nodules rarely harbour malignancy, if one is found that corresponds to the nodule in question, no cytologic evaluation is necessary

b. Warm that is tracer uptake is equal to the surrounding thyroid Ultrasound guided FNAC
c. Cold that is it has uptake less than the surrounding thyroid tissue - Ultrasound guided FNAC

Ultrasound thyroid:
Ultrasound thyroid is primary modality for evaluating thyroid nodule. The ultrasound thyroid should state the Size, Composition, Echogenicity, shape, Margins and Echogenic Foci.

(Table 1)

Ultrasound Thyroid Characteristics	Benign Features	Suspicious Features
Composition	Cystic	Solid
Echogenicity	Hyper/isoechoic, anechoic	Hypoechoic
Shape	Wider than tall	Taller than wide
Margins	Smooth, indistinct	Irregular
Echogenic Foci	None, Comet-tail	Punctate, echogenic foci, disrupted coarse Calcium

Table 1: Ultrasonographic features differentiating benign from suspicious nodules (6,7)

For risk stratification American ThyroidAssociation (ATA) risk stratifies nodule into five patterns based on imaging characteristics (Box 1) where as the American College of Radiology have developed a reporting system for thyroid nodules known as Thyroid Imaging Reporting and data System (TIRADS) (Box 2)

Box 1: Sonographic patterns, estimated risk of malignancy, and fine-needle aspiration guidance for thyroid nodules.2015 American Thyroid Association Management Guidelines for Adult patient with Thyroid Nodules and Differentiated Thyroid Cancer: The American thyroid Association Guidelines Taskforce on Thyroid nodule and Differentiated Thyroid Cancer (6)

Sonographic pattern	Ultrasound Features	Estimated risk of malignancy, %	FNA size cut-off (largest dimension)
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule ***with*** one or more of the following features: irregular margins (infiltrative, micro lobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of extrathyroidal extension	>7090%	Recommend FNA at =1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins ***without*** microcalcifications, extra thyroidal extension, or taller than wide shape	10-20%	Recommend FNAC at =1 cm
low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, ***without*** microcalcification, irregular margin or ETE, or taller than wide shape.	5-10%	Recommend FNAC at =1.5 cm
Very low suspicion	Spongiform or partially cystic nodules ***without*** any of the sonographic features described in low, intermediate, or high suspicion pattern	<3%	Consider FNAC at =2 cm Observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	<1%	No FNAC

Box 2: Five categories on the basis of American College of Radiology (ACR) Thyroid imaging, Reporting and Data System (TI-RADS). White Paper of the TI-RADS Committee (7)

Composition		Echogenicity		Shape		Margin		Echogenic Foci	
Cystic or almost completely cystic	0	Anechoic	0	Wider-than-tall	0	Smooth	0	None or large comet-tail artifacts	0
Spongiform	0	Hyperechoic or isoechoic	1	Taller-than-wide	3	Ill-defined	0	Macrocalcifications	1
Mixed cystic and solid	1	Hypoechoic	2			Lobulated or irregular	2	Peripheral (rim) calcifications	2
Solid or almost completely solid	2	Very hypoechoic	3			Extra-thyroidal extension	3	Punctate echogenic foci	3

Add points from all categories to determine TI-RADS score

Points	TI-RAD score	Sonographic Pattern	Risk of Malignancy	Recommendations
0 Points	TR1	Benign	0.3%	No FNAC
2 Points	TR2	Not suspicious	1.5%	No FNAC
3 Points	TR3	Mildly suspicious	4.8%	FNAC at = 2.5 cm *Follow up if =1.5cm
4 to 6 Points	TR4	Moderately suspicious	9.1%	FNAC at = 1.5 cm *Follow up if =1 cm
7 or more Points	TR5	Highly suspicious	35%	FNAC at = 1 cm *Follow up if =0.5cm

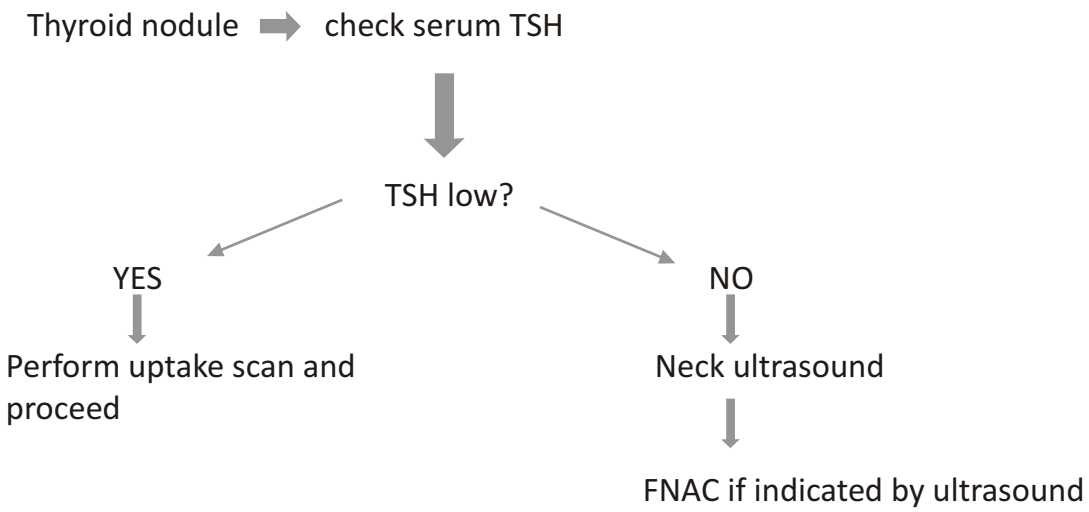
*For a TR5 lesion, we recommend scans every year for up to 5 years. For a TR4 lesion, scans should be done at 1, 2, 3, and 5 years. For a TR3 lesion, follow-up imaging may be performed at 1, 3, and 5 years. Imaging can stop at 5 years if there is no change in size, as stability over that time span reliably indicates that a nodule has a benign behaviour [8]

Recommendation:

It is very important that ultrasound thyroid must be reported using TI-RAD score or sonographic pattern described by ATA to streamline the practice. In Table 2, we have described ultrasound features and categorized them into ATA categories and TIRAD score.

ATA categories and recommendations	Ultrasound features	TIRAD score calculation and Recommendations
Benign No FNA	Pure Cyst	**TI-RAD 1** - No FNA Cystic (0)
Very low suspicious - FNA =2 cm	Spongiform Mixes solid/cystic Isoechoic solid area	**TIRAD 1, 2** No FNA Spongiform (0) Mixes solid/cystic (1) Isoechoic solid area (1)
Low suspicious FNA =1.5 cm	Partially cystic with uniformly solid isoechoic area Hyperechoic solid regular margins Isoechoic solid regular margins	**TIRAD 2** - observe Mixed solid cystic (1) Isoechoic (1) **TIRAD 3** FNAC = 2.5 cm *Follow up if =1.5cm -solid (2) - hyper-isoechoic (1)
Intermediate suspicious FNA =1 cm	Hypoechoic (2) solid (2) regular margins (0)	**TIRAD 4** FNAC = 1.5 cm *Follow up if =1cm -Solid (2) -Hypoechoic(2)
Highly suspicious features- FNAC = 1 cm	Hypoechoic, irregular margin Hypoechoic, irregular margin, punctate echogenic foci Hypoechoic, irregular margin, taller than wider Hypoechoic, extrathyroidal extension Suspicious left lateral lymph node	**TIRAD 4** - FNAC = 1cm Follow up if =1.5cm Hypoechoic (2) Irregular margin (2) **TIRAD 5** FNAC 1 cm or above Hypoechoic (2) Irregular margin (2) Punctate echogenic foci (3) Taller than wider(3) Extrathyroidal extension (3)

Table 2: ATA and American college of Radiology recommendations based on sonographic feature of thyroid nodule (6,7) *For a TR5 lesion, we recommend scans every year for up to 5 years. For a TR4 lesion, scans should be done at 1, 2, 3, and 5 years. For a TR3 lesion, follow-up imaging may be performed at 1, 3, and 5 years(8)



Conclusion:

Thyroid nodules are common. Thyroid ultrasound with survey of the cervical lymph node should be performed in all patients with known or suspected thyroid nodule. We propose a standardized ultrasound report using ATA sonographic features or TI-RAD system that may be helpful for endocrinologist dealing with thyroid nodule in their clinical practice and will avoid unnecessary FNAC.

Reference:

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Chapter 6

Thyroid & Pregnancy

Dr. Musarrat Riaz
Dr. Saima Askari

Key Points:

* Thyroid dysfunctions during pregnancy are associated with maternal and fetal complications
* Routine screening for thyroid dysfunction during pregnancy is not recommended at present.
* Newly diagnosed hypothyroidism during pregnancy should promptly be treated by Levothyroxine.
* Women already taking thyroxine prior to pregnancy require an increase of dosage by 30 to 50% at the start of pregnancy.
* Hyperthyroidism during pregnancy should be treated by anti-thyroid drugs after excluding **Transient Hyperthyroidism of Hyperemesis Gravidarum (THHG)**
* Sub clinical hypothyroidism should be treated in pregnancy so as to keep the TSH levels in reference range.

Introduction:

Thyroid diseases are second most common endocrine problems during pregnancy after diabetes. If left untreated, thyroid disorders may lead to significant maternal and fetal consequences including an increased risk of miscarriage and preterm delivery (1). During pregnancy, the size of the thyroid gland increases by 10% to 40% depending on whether there is endemic iodine deficiency present or not. Similarly, thyroid hormone production increases by around 50% (2). Common thyroid dysfunctions during pregnancy include hypothyroidism and hyperthyroidism. However, in some instances pregnancy may be complicated by thyroiditis, thyroid nodule and thyroid malignancy which needs close monitoring and appropriate interventions.

Etiology & Prevalence:

An estimated 23% of pregnant women are hypothyroid, out of which 0.30.5% have overt hypothyroidism while 22.5% present with subclinical hypothyroidism**.** Hyperthyroidism is reported in 0.10.4% of pregnant women (3)

Additionally, at least 510% of women are positive for thyroid antibodies which predisposes them to an increased risk of developing thyroid dysfunction during pregnancy

Normal Thyroid physiology during Pregnancy:

Thyroid gland undergoes many physiologic changes during pregnancy due to the increase metabolic needs of the body. Pregnant women tend to have lower serum TSH concentrations compared to the non- pregnant state. These physiologic changes are due to the following factors:

* Increase in the total T4 and total T3 concentrations due to an increase in serum thyroxine-binding globulin (TBG). (2)
* Human chorionic gonadotropin (HCG) which is produced during pregnancy stimulates TSH receptors resulting in increase in thyroid hormones production and subsequently suppressed TSH levels. (2)
* The thyrotropic activity of HCG also causes a decrease in serum TSH in the first trimester so that pregnant women have lower serum TSH concentrations than non-pregnant women.
* Thyroglobulin levels also increases during pregnancy reflecting an enhanced activity of the thyroid gland.

Thyroid function tests in Pregnancy: Normal values

American Thyroid Association (ATA) guidelines, states that serum TSH levels during pregnancy should be defined using population and trimester-specific based reference ranges. When population and trimester-specific normal ranges are not available, the ATA guidelines recommend that the upper limit for TSH should be 2.5 mIU/L in the first trimester, and 3.0 mIU/L in the second and third trimesters. Furthermore, the lower physiological limit could be 0.1 mIU/L in the first trimester, 0.2 mIU/L in the second, and 0.3 mIU/L in the third .

Screening:

Routine screening for thyroid dysfunction in pregnant women is not recommended. Current guidelines suggest a case-finding approach targeting thyroid function testing in high-risk groups. However, it should be remembered that undiagnosed hypothyroidism in pregnant women may adversely affect their fetuses therefore high-risk women should be timely evaluated.

Evaluation for thyroid dysfunctions during Pregnancy:

It should be remembered that not all pregnant women require thyroid evaluation.

Following are some of the conditions requiring thyroid evaluation**.**

* Women with goiter
* Signs & symptoms suggestive of thyroid dysfunction
* History of thyroid dysfunction in previous pregnancy
* History of pregnancy loss/pre-term delivery
* Family history of thyroid disorders
* TPOAb+
* Women with other autoimmune disorders

A thorough **history** focusing on signs and symptoms of thyroid disorders should be taken followed by complete **physical examination**. If signs and symptoms are suggestive of thyroid dysfunction the **Laboratory investigations** include TSH, T3 and T4 levels will help in categorizing women in one of the following categories.

Measurement of TSH is widely used because it is not only inexpensive but reliable and reproducible as well. However, evaluation of the results requires trimester specific reference ranges for pregnancy so as not to underestimate hypothyroidism and overestimate hyperthyroidism.

The presence of thyroid peroxidase antibody (TPOAb) with normal TFTs helps to identify the woman at increased risk of developing thyroid disease therefore, these women should be evaluated by checking the thyroid function once a trimester.

Management:

1-Hypothyroidism during Pregnancy:

The common causes are

* Iodine deficiency (in iodine deficient areas)
* Autoimmune thyroiditis (Most common cause in iodine sufficient areas)

Less common causes include

* radioiodine therapy,
* Prior thyroidectomy
* Use of antithyroid drugs
* Pituitary or hypothalamic diseases
* Congenital hypothyroidism

Pregnant women may present as either

Overt Hypothyroidism

* It is defined as increased trimester-specific TSH and *low* free T4 levels
* Untreated overt hypothyroidism results in maternal and fetal harmful consequences.

Complications of untreated hypothyroidism

Various obstetrical complications may occur secondary to untreated hypothyroidism (4)

* increased risk of spontaneous miscarriage,
* stillbirth and perinatal death.
* preterm delivery,
* fetal distress and
* increase in frequency of low-birth-weight infants

It is treated with thyroid hormone replacement so as to keep the TSH levels in trimester specific range. LT4 is the drug of choice for the treatment of hypothyroidism. The levels of TSH should be kept lower than 2.5 mIU/L during the first trimester, and it should not exceed 3.0 mIU/L during the second and third trimester.(4)

Most women (50% to 85%) with pre-existing hypothyroidism before pregnancy needs 30% more thyroid hormone to keep the TSH levels in trimester specific range.

Sub clinical Hypothyroidism (SCH)

* It is defined as increased trimester specific TSH and *normal* free T4 levels
* It is usually an asymptomatic condition but occasionally can presents with mild symptoms of hypothyroidism, such as fatigue and constipation**.**
* SCH can also cause various obstetrical problems just like overt hypothyroidism especially higher rate of fetal death than controls. However still routine screening and treatment of subclinical hypothyroidism during pregnancy is not recommended.
* ATA recommends that it should be treated in females with positive TPO antibodies and TSH greater than 2.5 mU/L

Management of Hypothyroidism during Pregnancy:

* Once the diagnosis is established, the treatment should be initiated as soon as possible.
* The starting dose of levothyroxine is 12 microgram/kg/day taken on an empty stomach, is the treatment of choice and should be adjusted every 4 weeks.
* Women who are diagnosed before pregnancy and is already taking treatment should increase their dose by approximately 3050%.
* As the pregnancy advances, the requirement of levothyroxine increases mainly due to the increase demand plus decrease absorption secondary to ferrous sulphate replacement.(5)
* After delivery the dose of levothyroxine needs to be decreased to pre-pregnancy level.
  Thyroid function tests should be repeated after 6 week post partum to further adjust the dose of levothyroxine.

Hyperthyroidism during Pregnancy:

* Hyperthyroidism is defined as an excessive production of thyroid hormones.
* It is less common compared to hypothyroidism during pregnancy.
* The signs and symptoms of hyperthyroidism may sometimes be masked by the normal physiologic changes in pregnancy.
* Untreated severe hyperthyroidism can lead to increased risk of stillbirth, preterm delivery, intrauterine growth retardation, preeclampsia, spontaneous abortion and heart failure. (6)
* Signs and symptoms include tachycardia, heat intolerance, weight loss, tremors which often is difficult to distinguish from the physiological changes during pregnancy.
* HCG stimulation on the TSH receptor results in worsening of the symptoms during first trimester.
* Symptoms usually improves in second half of pregnancy resulting in decrease requirement of anti-thyroid drugs.
* Goiter is usually present during pregnancy.
* Eye signs including ophthalmopathy can be observed after careful evaluation.

Laboratory evaluation:

* Laboratory evaluation includes determination of serum TSH, FT4 and Thyroid Receptor Antibodies (TRAb) levels.

Differential diagnosis:

Transient Hyperthyroidism of Hyperemesis Gravidarum (THHG)

* It is defined as transient hyperthyroidism, characterized by elevated serum FT4 and suppressed or undetectable serum TSH, limited to the first trimester of pregnancy, in the absence of thyroid autoimmunity (7).
* As the pregnancy progresses, serum FT4 normalized spontaneously by the end of first trimester; however TSH levels may remain suppressed for many more weeks.
* Antithyroid drugs are usually not required for treatment.

Sub clinical hyperthyroidism

* It is defined as suppressed serum TSH concentration below the lower limit of reference range, with normal FT4 and FT3 concentrations.
* It is generally not associated with adverse pregnancy outcomes, therefore requires no treatment.

Management of hyperthyroidism during pregnancy When to treat?

* Symptomatic, moderate/severe overt hyperthyroidism

Treatment not required

* Transient Sub Clinical Hyperthyroidism in first trimester
* GTThcg mediated overt hyperthyroidism
* Hyperemesis gravidarum associated hyperthyroidism
* Subclinical, mild & asymptomatic but biochemically overt hyperthyroidism
* Hyperthyroidism during pregnancy is usually managed by anti-thyroid drugs (ATD).
* The aim of management is to keep the patient euthyroid using the lowest dose of antithyroid drugs to keep the FT4 levels just above the range or in the upper two third of normal reference range.
* Excessive amount of ATDs may lead to hypothyroidism.
* The dose of ATD need to be adjusted every 4-6 week.
* Beta blockers like propranolol or atenolol can be used to control the adrenergic symptoms of thyrotoxicosis.
* Propranolol in a dose of 10-40 mg 6-8 hourly can be used.

Anti-thyroid drugs Propylthiouracil (PTU):

* The treatment of choice is propylthiouracil (PTU) in pregnancy.
* PTU is given in a dose of 100450 mg/day in divided doses.
* Dose may need to be adjusted after 2-4 weeks depending on the response.
* Although well tolerated PTU shows a higher incidence of hepatotoxicity
* The present recommendation by the American Thyroid Association is to use PTU during the first trimester only, and to switch to MMI in the second and third trimesters

Methimazole (MMI):

* MMI is used in pregnancy during second and third trimester.
* It can be prescribed at 1020 mg/day.
* MMI has been associated with aplasia cutis and choanal/esophageal atresia, occurring with other congenital defects, including hearing loss, dysmorphic facial features, and developmental delay known collectively as “methimazole embryopathy”

Surgery:
In patients allergic to ATDs thyroidectomy can be performed.

Radioactive iodine therapy (RAI):
RAI therapy is **CONTRAINDICATED** during pregnancy and lactation.

Fetal and Neonatal outcomes of hyperthyroid mothers:

* Maternal overtreatment with ATD may produce fetal goiter and hypothyroidism. Fetus may develop polyhydramnios. Decreasing the dose of ATD will help in resolving the goiter.
* Infants born to mothers who are not treated for hyperthyroidism may present with congenital hypothyroidism with inappropriately low TSH and Low T4 probably caused by maternal T4 crossing the placenta barrier that suppressed fetal TSH. This condition resolves within few weeks without any treatment.
* Fetal thyroid gland may be stimulated by circulating maternal TRAB levels leading to fetal hyperthyroidism
* Tachycardia, fetal growth retardation, fetal goiter, hydrops, and accelerated fetal bone maturation are some of the signs of fetal hyperthyroidism and should be treated by anti-thyroid drugs.

Thyroid Nodule & Pregnancy:

* Thyroid nodules may present because of the stimulatory effects of estrogen, progesterone, hCG and iodine deficiency.
* Evaluated in the same way as in non -pregnant state
* TSH followed by ultrasound should be performed.
* Radionuclide scanning is contra indicated.
* FNAC may be performed if indicated (Newly diagnosed nodule with non- suppressed TSH)
* If surgery is required optimal timing is second trimester

Post-partum Thyroid dysfunction:
During post-partum period thyroid dysfunctions may present in one of the following ways

* Postpartum thyroiditis
* Graves' disease (Already discussed)
* Exacerbation of Hashimoto's Thyroiditis (Already discussed)

Postpartum thyroiditis: (8,9)
Postpartum thyroiditis (PPT) is an immune mediated inflammation of the thyroid gland that affects approximately 1 in 14 women during the first year (usually within 6 months, typically 2 to 4 months) after delivery.

The occurrence of PPT reveals the immune suppression occurring during pregnancy and consequently the rebound of the immune system in the postpartum period. Females having other autoimmune diseases are at increased risk of PPT. Particularly, the prevalence of PPT is 25% with T1DM, 14% with SLE, and 44% with a past history of Graves' disease. Moreover women who had a prior history of PPT and who have returned to the euthyroid state still have a 70% chance of developing PPT in the following pregnancy.

Clinical presentations:

Three types of clinical presentations have been recognized for PPT are as following:

(1) Transient hyperthyroidism (32%),

(2) Transient hypothyroidism (43%), and

(3) Transient hyperthyroidism followed by hypothyroidism and then recovery, the classic form of PPT (25% of patients).

Symptoms of PPT:

The hyperthyroid phase has usually no symptoms or only milder ones. Symptoms may include tachycardia, palpitation, irritability, heat intolerance, insomnia, tiredness etc.

Symptoms of the hypothyroid phase may be mistaken for the "baby blues/postpartum blues". **Postpartum blues** is a mild and short-term mood disorder that results after pregnancy, the most common type of **postpartum** depression. The symptoms of hypothyroidism may include cold intolerance; dry coarse skin; constipation; impaired concentration; paresthesia; among others.

Evaluation and diagnosis:

The diagnosis of postpartum thyroiditis mainly depends on the clinical presentation and thyroid function tests (TSH and FT4). PPT has similar biochemical findings that can be occurred in painless thyroiditis: low serum TSH level and high/normal serum FT4 and T3 levels in the hyperthyroid phase, which might be subclinical or overt.

In hypothyroid state preceded by hyperthyroid phase , T4/T3 level could be low for days to weeks before TSH level rises above normal, resulting from prolonged suppression of TSH in hyperthyroid state.

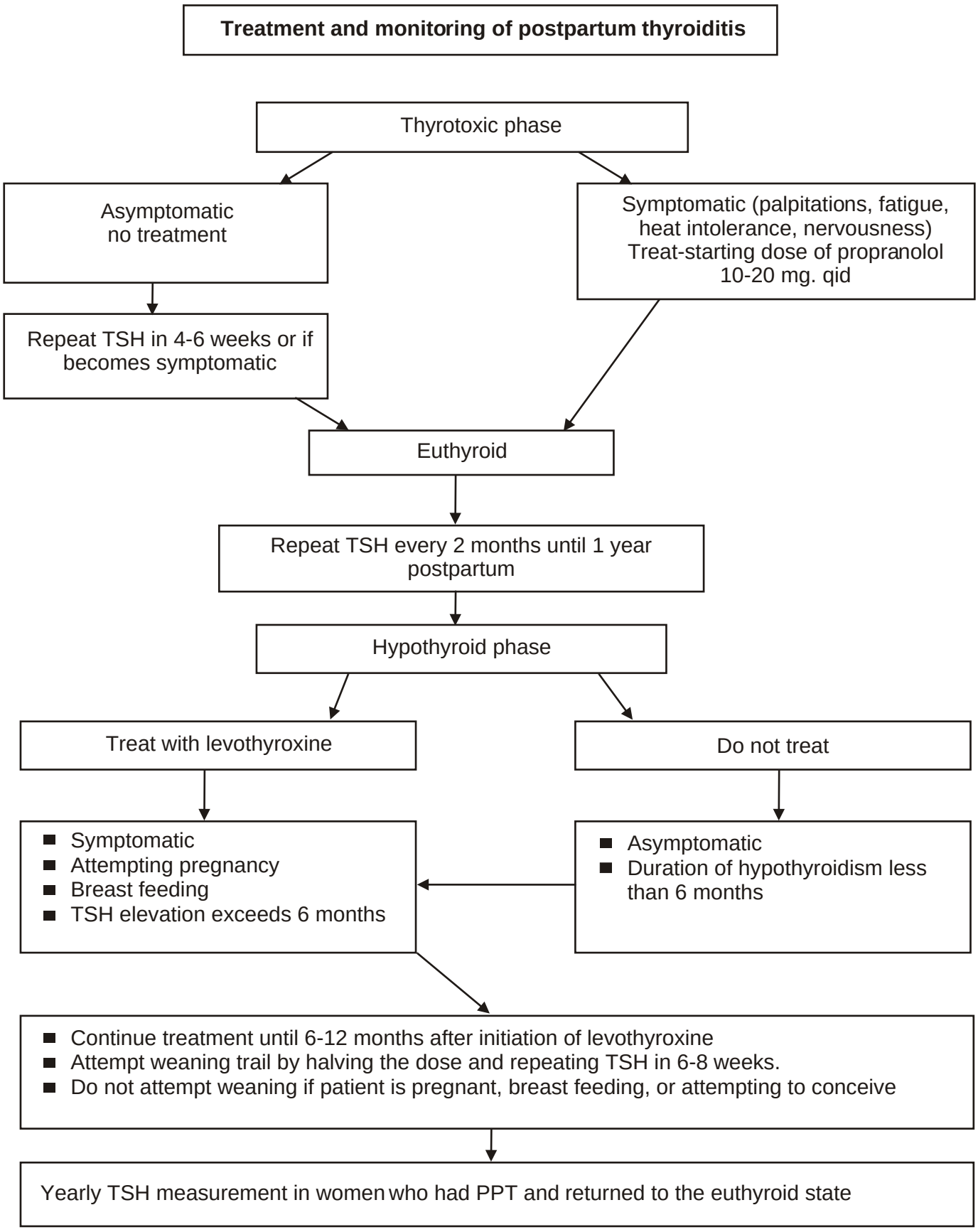
Serum levels of anti-TPO antibodies/anti-thyroglobulin are high in PPT and are highest in the hypothyroid state or soon thereafter. Some of the women may have a slight increase in C-reactive protein and/or ESR.

How to manage:

The hyperthyroid phase of PPT rarely needs treatment. If symptoms are bothersome to patient, a beta-blocker will be sufficient to alleviate symptoms. The lowest effective dose of beta blocker should be used. ATD are not indicated in PPT.

The hypothyroid phase of PPT if patient is asymptomatic and or duration of biochemically hypothyroid is < 6 months treatment is not necessary. However if patient is symptomatic, breast feeding, trying to conceive and or biochemically hypothyroidism exceeds 6 months, thyroxine replacement therapy is indicated.

Management of postpartum thyroiditis is typically transient, with trial to discontinue treatment 612 months after the initiation of levothyroxine, unless the patient is pregnant, breastfeeding or trying to become pregnant. Moreover, Postpartum thyroiditis may lead to permanent hypothyroidism in > 50% of all women and annual TSH monitoring is indicated to those with prior history of postpartum thyroiditis.


Treatment and monitoring of postpartum thyroiditis
Thyrotoxic phase
Asymptomatic
no treatment
Symptomatic (palpitations, fatigue, heat intolerance, nervousness)
Treat-starting dose of propranolol
10-20 mg. qid
Repeat TSH in 4-6 weeks or if becomes symptomatic
Euthyroid
Repeat TSH every 2 months until 1 year postpartum
Hypothyroid phase
Treat with levothyroxine
Do not treat
Symptomatic
Attempting pregnancy
Breast feeding
TSH elevation exceeds 6 months
Asymptomatic
Duration of hypothyroidism less than 6 months
Continue treatment until 6-12 months after initiation of levothyroxine
Attempt weaning trail by halving the dose and repeating TSH in 6-8 weeks.
Do not attempt weaning if patient is pregnant, breast feeding, or attempting to conceive
Yearly TSH measurement in women who had PPT and returned to the euthyroid state

An algorithm for the treatment and monitoring of postpartum thyroiditis.

Post partum care and surveillance:
Postpartum care of Hypothyroid women:

Mostly women with hypothyroidism may resume their pre-pregnancy levothyroxine dose in postpartum, with measurement of TSH levels every 4 to 6 to ensure euthyroidism.

However, women with positive antithyroid antibodies are at increased risk of exacerbation of autoimmune thyroid dysfunction in postpartum, and > 50% of women with Hashimoto's thyroiditis still require increased doses of levothyroxine in the postpartum period.

Females having subclinical hypothyroidism during pregnancy may not require levothyroxine treatment during the postpartum period, unless hypothyroid phase of postpartum thyroiditis ensues or the woman is again planning to conceive.

Postpartum care of Hyperthyroid women:

Females having prior history of Graves' disease or hyperthyroidism taken treatment during gestation are at increased relapse risk during the postpartum. Moderate dose of antithyroid drugs (ATD) is safe during breastfeeding and has not been shown to affect development of the infant.

Lactation with thyroid disorder:

Beta blockers:

Certain beta-blockers are safe to use during breastfeeding because only a small amount is excreted in breast milk. However, the lowest effective dose is best.

Anti-thyroid drugs:

Lactation has been shown to be safe in mothers taking ATDs in low-to-moderate doses. They excrete in breast milk in very small concentrations and the lowest effective doses possible should be used with maximal doses of Methimazole 20 mg daily.

However, as a safety concern infants of mothers taking ATD during lactation need to be screened with thyroid function tests. ATD dosage should be split into 2 to 3 divided doses and administered immediately after feeding.

Radioactive iodine (RAI) is contraindicated in lactation.

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Chapter 7

Surgical Call For Thyroid Disorders

Dr. Shair Zaman
Dr. Mujeeb Ur Rehman

While dealing with patients of thyroid disorders, there are multiple treatment options depending upon the patient's diagnosis. These include

* medications needed to treat hypo or hyperthyroidism,
* radioactive iodine treatment for hyperthyroidism and at times for malignancy and
* surgical options.

Surgical call for thyroid diseases is well understood in cases of malignancy as the tissue involved and associated lymph nodes need dissection. There are, however, some indications for benign thyroid diseases as well. This chapter is aimed to discuss the concept of surgical indications.

Case scenario:

A 42-Year-old Lady presented to you with a painless swelling in front of her neck, that is firm and irregular. She feels it's more on the right side and moves with swallowing. She noticed it for the first time 8 months ago but was ignoring it. She also complains of on & off constipation for which she had been using home remedies like Ispaghul husk. Upon further questioning, she feels lethargic, sleepy, cold and energy less most of the time.

On examination, multinodular goiter, firm in consistency is noticed with distended neck veins but Pemberton test performed is negative. Her pulse was 70 betas per minutes and skin and hair were dry.

She was advised thyroid function tests (TFTS) and ultrasound neck. Her TFTS were suggestive of primary hypothyroidism with TSH of 60. Her ultrasound showed bilateral nodules, two of which were fulfilling the need for fine needle aspiration cytology (FNAC). She was started on Tab Thyroxine 50mcg daily and advised to follow with FNAC result.

Common symptoms at presentation

* Swelling in front of the neck, diffuse or nodular that might be noticed by patient or relatives/friends.
* Symptoms can range from nothing except swelling to, discomfort, pain and associated fever depending upon underlying cause.

Common signs at presentation

* Signs depend upon underlying cause like tenderness and redness in thyroiditis
* Vocal cord paralysis, and/or hoarseness
* Cervical lymphadenopathy
* Fixation of the nodule to surrounding tissue
* Obstructive symptoms like engorged neck veins (SVC obstruction).
* Pemberton sign: it is the engorgement of the neck veins upon upper arm elevation. This is performed to know thoracic inlet compression by large plunging goiter. It can be manifested with any neck swelling and in case of goiter, its a clinical sign to show thoracic extension (1).

Pertinent points in history

History needs to be aimed at the following points

1. Duration of the swelling
2. Any pain associated with swelling or new pain arising from already existent goiter and/or sudden or rapid increase in size points to hemorrhage in the nodule or due to possible malignancy.
3. Family history of goiter as multinodular goiter is familial at times or some types of thyroid malignancy runs in families (medullary carcinoma).
4. People living in hilly areas (Chitral) have endemic goiter due to low iodine intake.
5. Childhood head and neck radiation therapy.
6. Total body radiation for bone marrow transplantation.
7. Exposure to ionizing radiation in childhood or adolescence.
8. Familial thyroid carcinoma, Thyroid cancer syndromes (e.g., PTEN hamartoma tumor syndrome [Cowden's disease], FAP, Carney complex, Werner syndrome/progeria, or MEN 2.
9. A risk for medullary thyroid cancer [MTC]) in a first degree relative.

Indications for surgical call (2)

Surgical call for thyroid disease is needed in some cases, e.g.

1. Confirmed malignancy or a thyroid nodule with Bethesda score 4 and 5.
2. Pressure symptoms:

a) Respiratory symptoms i.e., Stridor
b) Cardiovascular symptoms i.e., SVC syndrome

3. Cosmetic issue especially in young patients
4. Some patients with Graves' disease may need surgery as definitive therapy especially in some difficult cases with thyroid associated orbitopathy.
5. Conditions such as Graves or MNG where RAI is indicated but declined due to fear of radiation or antithyroid drugs intolerance.
6. Coexisting hyperparathyroidism
7. Amiodaron associated thyrotoxicosis where it's not responding to initial treatment and Amiodarone need to be continued.

Patient needing surgical intervention may present as hypo, hyper or euthyroidism. Thyroid activity status may delay the surgery but patient can present with any of them.

Contraindications for surgery

Cardiopulmonary disease
End-stage cancer
Other debilitating disorders

Differential diagnosis of neck swelling (Goitre)

Goiter can be easily detected on clinical examination and usually there is no ambiguity or confusion in most of the cases. However, following points should be noted for differential diagnosis.

1. Parathyroid adenoma, usually not palpable unless carcinoma of parathyroid.
2. Thyroglossal cyst
3. Branchial cyst
4. Neck/ thyroid abscess
5. Sarcoma
6. Lipoma
7. Lymph nodes, at times are so large that confusion arise in differentiation like Kikuchi lymphadenitis.

Diagnostic tests

1. **Thyroid function test**

* The first tests that need to be done is TSH and ultrasound scan to know thyroid activity status as rest of the investigations depend upon this test.
* If the serum **TSH is subnormal**, a radionuclide thyroid scan should be performed.
* If the serum **TSH is normal or elevated**, a radionuclide scan should not be performed as the initial imaging evaluation.

2. **Ultrasound Neck and Doppler for Thyroid**

* Ultrasound is very important tool to decide about the future course of the thyroid swelling. Based on criteria, decision is made to proceed with FNAC or not. American thyroid association (ATA) have established criteria for that (table 1). In general, following points are important in ultrasound report.
* nodule size
* location (e.g., right upper lobe)
* composition (solid, cystic proportion, or spongiform)
* echogenicity
* margins
* presence and type of calcifications
* shape if taller than wide
* vascularity.

3. **FNAC to rule out malignancy if needed**
4. **Scintigraphy of the thyroid for those having hyperthyroidism**
5. **CT scan chest** is needed when there is large goiter and have retrosternal extension and tracheal compression.
6. **Respiratory flow loop** specially for large goiter.

Management

Toxic Multi nodular goiter:

The first line of treatment for toxic multi nodular goiter is either radioactive iodine ablation or anti-thyroid drugs. Hoverer, surgery is required for toxic MNG when goiter size is large enough to cause symptoms like pressure effects/obstruction. Patient should be first rendered euthyroid with medical therapy.

Non-Toxic Multi nodular goiter:

Nontoxic multinodular goiter, when patients is having goiter and thyroid functions tests are normal, is generally followed without need for surgery. However, when patient has goiter large enough to cause compression symptoms then surgery can be advised. Surgery is needed for cosmetic reasons as well even without pressure symptoms.

Differentiated thyroid malignancy:

Total thyroidectomy with neck dissection is needed for these patients to have complete removal of the malignant tissue. Sometimes lobectomy is done if disease is restricted to single lobe and no extension to the other lobe.

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Chapter 8

Multidisciplinary Approach For Thyroid Disorders

Dr. Ibrar Ahmad
Dr. Tahir Ghaffar

The Need for Multidisciplinary Approach In Management of Thyroid Disorders

Effective diagnosis and treatment for thyroid disorders and thyroid cancers involves input from a variety of specialists. As thyroid gland can present with variety of disorders from simple goiter to overactive or underactive gland, autoimmune disorders, thyroiditis and thyroid cancers. So, to have a consensus and uniform approach on the management of thyroid disorders there is a need for multidisciplinary approach for the management of these disorders.

The Multidisciplinary Thyroid Management Team

- Brings together team members who are leading experts in their specialties for thyroid.
- Designs personalized treatment plans using the latest medical techniques and advanced surgical methods.
- Offers access to novel molecular diagnostic testing of thyroid nodules and tissues.
- Provides advanced thyroid cancer patients with access to cutting-edge cancer therapies and clinical trials.

Several types of healthcare providers can play a role in managing thyroid disease and its symptoms. Some people only see one healthcare provider for thyroid-related issues, while others have a medical team who, work together to manage their thyroid disorder. The type of healthcare providers in the team include:

- Endocrinologist
- Otolaryngologist/Head & Neck Surgeon
- Ophthalmologist/Oculoplastic Surgeon
- Medical Oncologist & Nuclear Medicine Specialist

THYROID DISORDERS

Problems with the thyroid gland include too much (hyperthyroidism) or too little (hypothyroidism) thyroid hormone, inflammation of the thyroid gland (thyroiditis), thyroid nodules (lumps in the thyroid gland), or thyroid cancer.

Role of Endocrinologist

When thyroid disorders cannot be managed by a general practitioner then an endocrinologist consult is needed. Patient can present with a wide variety of signs and symptoms. Ordering correct investigations and clinching the correct diagnosis in such cases can be quite challenging. Pregnancy related thyroid issues are also dealt by endocrinologists.

Common thyroid disorders managed by endocrinologists include; hyperthyroidism, hypothyroidism, thyroiditis and thyroid nodules. These can be treated by simple medications and regular follow-up. Thyroid medications are used to restore patient to a euthyroid state and to maintain this for a prolonged period in the hope that a permanent remission of disease will occur. However, if the cases are complicated, then other specialists are consulted.

Role of Otolaryngologist/Head & Neck Surgeon

Sometimes, the thyroid gland becomes so enlarged that it compresses the airway. It becomes difficult for patient to breathe as well as swallow. In such scenario, medications alone are not sufficient. And surgery can be considered for symptoms relief as well as for cosmetic appearance. If patient grave's disease is not responding to anti thyroid drug treatment or radioactive iodine ablation or their multiple relapses of the disease, patient is then referred to an otolaryngologist/head & neck surgeon.

Advantage of surgery is that the goiter is removed, the cure is rapid and the cure rate is high if surgery has been adequate. However, there is a risk of permanent hypothyroidism, hypoparathyroidism and nerve injury.
If after surgery patient develops hypoparathyroidism or hypothyroidism, then an endocrinologist consult is needed.

Role of Ophthalmologist (Oculoplastic Surgeon)

Graves ophthalmopathy is one of the serious complications of Graves Diseases. Mild symptoms of Graves' ophthalmopathy may be managed by using over-the-counter artificial tears during the day and lubricating gels at night. However, if the symptoms are severe then an ophthalmologist consult is taken. An ophthalmologist may recommend Corticosteroids or Teprotumumab. And if the pressure on the optic nerve is severe and threatens the loss of vision, then the patient might need orbital decompression surgery.

Role of Medical Oncologist

Thyroid cancer is the 5th most common cancer in women and the 16th most common cancer in men. The diagnosis of thyroid cancer is usually made by fine-needle aspiration cytology (FNAC) of a thyroid nodule. Ideally treatment for thyroid cancer should involve a thyroid cancer specialist team (endocrinologist, oncologist, head & neck surgeon) Endocrinologists are the primary treating physicians for thyroid cancer. Oncologists can assist the endocrinologist when targeted chemotherapies are needed for the rare aggressive thyroid cancers.

Role of Nuclear Medicine (Radiotherapy)

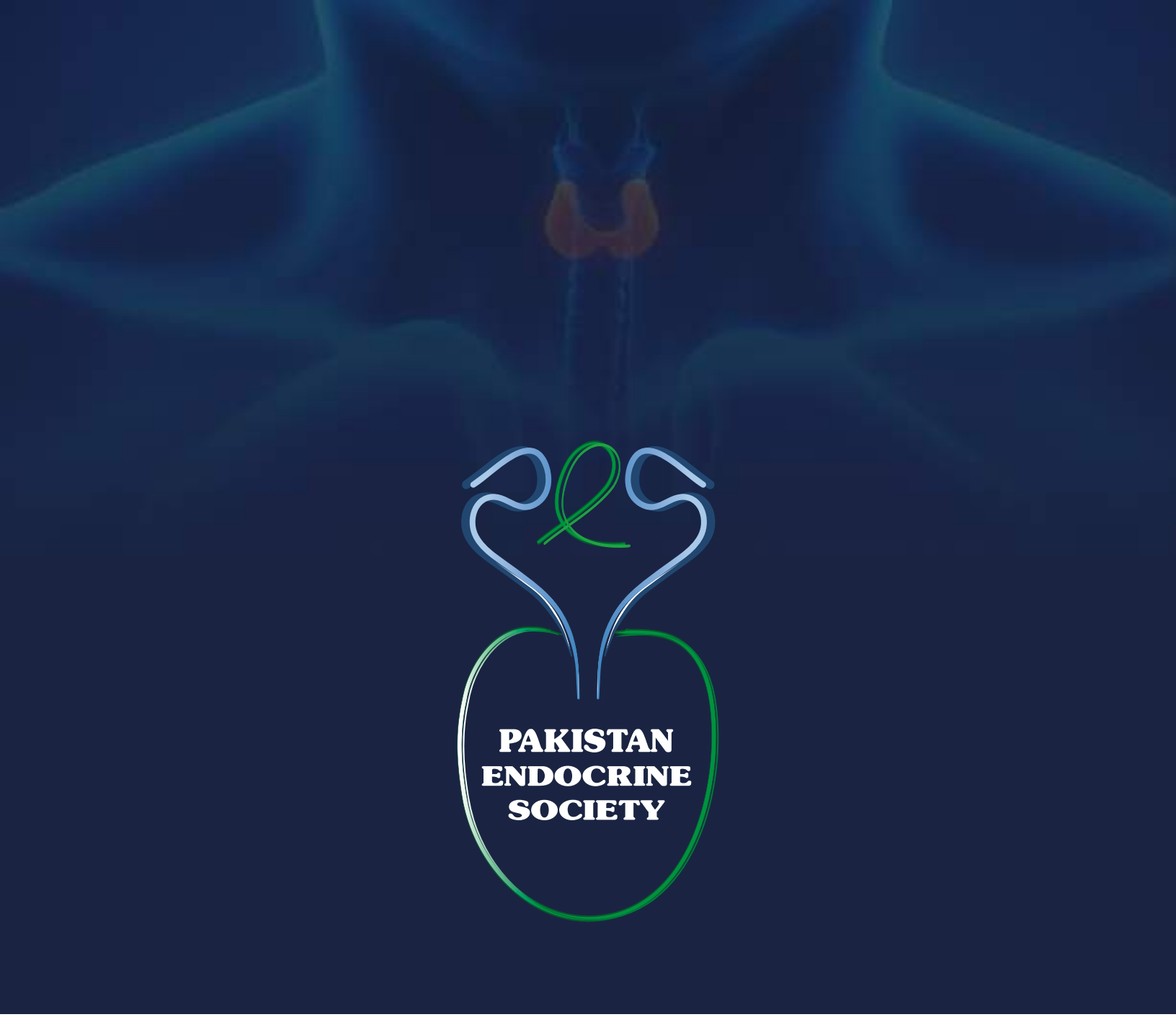
Thyroid cancer is treated by surgical removal, but sometimes requires additional treatment with radioactive iodine.

For management of such patients a nuclear medicine team in consulted. The dosages of radioactive iodide in thyroid cancer are much higher than with hyperthyroidism treatment. The therapy is usually given after removal of the thyroid gland to destroy any remaining thyroid tissue. However, there is a risk of permanent hypothyroidism. Also, radiotherapy is contraindicated in pregnant patient and in such patient's other treatment options are considered.

Therefore, patient with thyroid disorders require comprehensive treatment and it can only be provided if a multidisciplinary team approach is adopted. The team includes specialists recognized in their expertise in treating the most challenging cases. And with this approach, overall, the Patient Outcomes are Better!

The End

Thyroid Disorders: A Practical Approach is a gift from Pakistan Endocrine Society for our General Practitioners and Internist. This will improve the practices of our fellow Health Care Processionals. An endeavor which will be followed in future.



PAKISTAN ENDOCRINE SOCIETY

Fazaia Ruth Pfau Medical College
PAF Base, Faisal,
Main Shahrah-e-Faisal Karachi - Pakistan

Shaukat Khanum
Memorial Cancer Hospital
and Research Centre

Farooq Hospital

THE AGA KHAN UNIVERSITY

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