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Review Article

RECENT TRENDS AND THERAPEUTIC APPROACHES OF THYROIDISM ON INFERTILITY

Undamatla Bhargavi*, Draksharapu Nandini, Vendra Sri ramani naga vignavi, Natha Venkat kiran, Lankapalli Bhagya sri, Gandi satya Krupa.

*M.pharmacy (pharmacology), Assistant professor, Dr.c.s.n institute of pharmacy, Bhimavaram-534201

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ABSTRACT:

Thyroid disorders are the most common endocrine problems in women. In most of the cases, thyroid can lead to infertility or miscarriages. The etiology of infertility is multifactorial with thyroid disorders as the most common presenting factor, hypothyroidism in particular. Infertility in women can lead to emotional and psychological stress. The prevalence of hypothyroidism during pregnancy is estimated to be 0.3%–0.5%. Hypothyroidism and hyperthyroidism can result in menstrual irregularities and anovulatory cycles, thus affecting the fertility. There is a) level in infertile women with hypothyroidism when compared to euthyroid patients, indicating the relation between hypothyroidism and hyperprolactinemia. The amount of thyrotropin releasing hormone (TRH) from the hypothalamus is markedly increased by inhibition of pyroglutamyl peptidase II, the enzyme catalyzing TRH. The increased TRH in hypothyroidism causes increased thyroid-stimulating hormone and PRL secretion by pituitary, leading to infertility and galactorrhea. In recent years, a neuropeptide called kisspeptin, encoded by Kiss1 gene, a potent stimulus for GnRH secretion, has been recognized, which suggests a future direction of treatment with kisspeptin and benefits the fertility induction among hyperprolactinemic infertile patients. Untreated hypothyroidism during pregnancy can lead to subfertility, fetal deaths, premature deliveries, and abortions. Therefore, women planning for pregnancy and infertile women should be assessed for thyroid hormones and serum PRL.

INTRODUCTION

1. DEFINITION

Thyroid:

Thyroid is a small butterfly shaped gland located at the front of your neck under your skin. it is a part of endocrine system and controls many of your functions by producing and releasing certain hormones. The main function is to control the speed up of your metabolism process of transforming the food into energy.

Hypothyroidism:

Hypothyroidism is when your thyroid gland doesn't make and release enough thyroid hormone into your blood stream. This condition slows down your metabolism which may make you gain weight unexpectedly or feel tired all the time.

Hyperthyroidism:

Hyperthyroidism is a medical condition where the thyroid gland produces excess thyroid hormone, leading to an overactive metabolism.

Address for Correspondence: Undamatla Bhargavi, M.pharmacy (pharmacology), Assistant professor, Dr.c.s.n institute of pharmacy, Bhimavaram-534201, Mail: nandinidraksharapu@gmail.com

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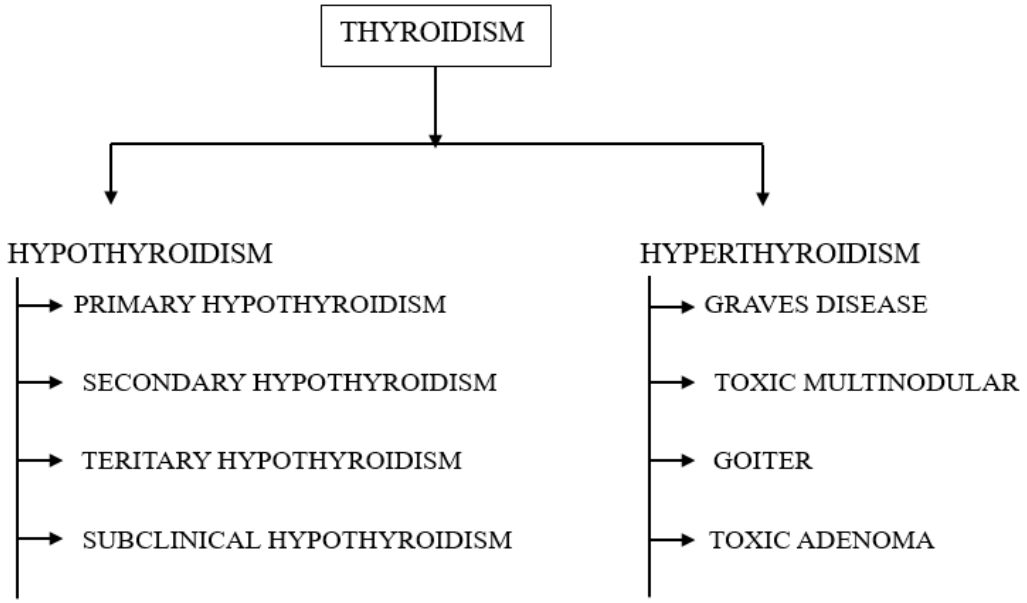
2. TYPES:



3. HISTORY

The history of hypothyroidism dates back to ancient times, with descriptions of thyroid-related disorders found in Hindu texts as early as 0300 BC and in the works of Hippocrates. the condition was better understood until the late 19th century.

Ancient Times:

- Early descriptions: Thyroid gland descriptions date back to ancient civilizations, such as the Egyptians and Greeks.
- Treatment: Early treatments included iodine-rich substances, like seaweed.

19th-20th Centuries:

- Thyroid extract: Thyroid extract was used to treat hypothyroidism.
- Surgical advancements: Thyroid surgery became more common and safer.

Mid-20th Century:

- Radioactive iodine: Introduced for treating hyperthyroidism and thyroid cancer.
- Thyroid hormone synthesis: Synthetic T4 (levothyroxine) was developed.

Modern Era:

- TSH testing: Thyroid-stimulating hormone (TSH) tests became widely available.
- Refined treatments: More precise dosing and treatment options.
- Increased awareness: Greater understanding of thyroid disorders and their impact on health.

Ongoing Research:

- Genetic studies: Research on genetic factors contributing to thyroid disorders.
- New treatments: Development of novel therapies and targeted treatments. The understanding and management of thyroid disorders continue to evolve, improving patient outcomes.

Key Milestones- Early Descriptions:

- 150 ADS: Hippocrates and Plato recognized the treatment of goiter using burnt sponge and seaweed.
- 1656: Thomas Wharton named the thyroid gland.

Understanding the Condition:

- 1873: Sir William Withey Gull provided a clinical description of myxoedema; a condition associated with hypothyroidism.
- 1878: William Ord coined the term "myxoedema" and described the pathological changes associated with the condition.

Treatment Developments:

- 1891: George Redmayne Murray introduced thyroid extract treatment for hypothyroidism.
- 1914: Purified thyroxine was introduced.
- 1920s-1930s: Synthetic thyroxine became available.
- 1950s: Synthetic thyroid medications, such as levothyroxine, became widely used.

Landmark Discoveries- Iodine's Role:

- 1851: Charles Chatin discovered the link between iodine deficiency and goiter.

- 1883: Eugen Bauman found an iodine compound in the thyroid gland.

Hormone Regulation:

- 1915: Edward Kendall isolated thyroxine.
- 1952: Liothyronine (T3) was identified.
- 1970: Peripheral conversion of T4 to T3 was discovered.

Advances in Diagnosis:

- 1971: TSH radioimmunoassay was developed.
- 1972: T3 and T4 radio immune assays were developed.

4. GLOBAL BURDEN:

1. The global prevalence of congenital hypothyroidism (CH) among neonates from 1969 to 2020 was between 1969 and 2020.
2. The pooled global prevalence of CH from 1969 to 2020 was found to be 4.25.
3. Region-wise, the prevalence was highest in the Eastern Mediterranean region 7.49, followed by Europe 2.48, and upper middle-income countries 6.76.
4. The global prevalence of CH increased by 52.1% during 2011–2020 compared to 1969–1980.
5. Prevalence by region was reported as follows:
Africa: 14.2
Oceania: 11.0
South America & Europe: 6.8
North America & Asia: 5.8.
6. The Global Burden of Disease (GBD) 2010 project, which evaluated diseases across age groups and countries over the period 1990–2010, provides insight into the impact of thyroid disease at a global scale
7. Mortality from thyroid cancer increased by 50.2%, rising from ~24,000 deaths
8. (95% uncertainty interval: 18,000–29,900) in 1990 to ~36,000 (26,000– 43,200) in 2010, mirroring trends of overall cancer and NCD mortality increases.
9. In terms of ranking, thyroid cancer in South Asia is the 94th cause of death overall (and 90th among women), while globally it ranks 92th (81st in women).
10. Deaths due to iodine deficiency also rose from about 2,000 (1,700–2,400) in 1990 to 3,400 (2,400–3,800) in 2010 an increase of ~67.7%.
11. This is notable, as deaths from many nutritional causes showed a decreasing trend over the same period.
12. While thyroid diseases seldom directly cause death, their complications and downstream effects contribute substantially to disability.
13. goiter stemming from iodine deficiency accounts for about 2.72% of global disease sequelae a proportion comparable to that of “uncomplicated diabetes mellitus” (3.30%) and exceeding that of conditions like polycystic ovarian syndrome (1.68%).
14. There are a gender disparity goiter affects females more (3.44%) than males (2.01%).
15. Over the two decades studied, both goiter and heart failure from iodine deficiency showed increases in the years lost to disease (YLD) by ~29.8% and 33.3%, respectively.
16. Intellectual disability due to iodine deficiency (previously labelled “idiopathic”) declined by ~58.4%, from 271,000 years in 1990 to 113,000 in 2010.
17. In terms of disability-adjusted life years (DALYs), thyroid cancer led to ~836,000 DALYs in 2010 a 44.4% increase from 579,000 in 1990.
18. Iodine deficiency contributed to a shifting burden globally, it ranked 85th among causes of DALYs and 79th in South Asia, but in Central Sub-Saharan Africa it rose to 43th position.
19. Among women, iodine deficiency occupied ranks 74 globally, 70 in South Asia, and 35 in Central Sub-Saharan Africa in the DALY rankings.

State-wise Prevalence:

- Kerala: 15.8% of women having thyroid dysfunction.
- Jammu & Kashmir: The Himalayan region, including J&K, reports higher cases of thyroid disorders, possibly due to iodine deficiency.
- Delhi: Delhi shows a prevalence of 11.07% hypothyroidism, with undetected cases significantly higher (3.97%).
- Kolkata: Kolkata records the highest prevalence of hypothyroidism (21.67%) among studied cities.

City-wise Prevalence

Ahmedabad: 10.61% prevalence of hypothyroidism.
Bangalore: 9.23% prevalence.
Chennai: 9.77% prevalence, with 2.09% undetected.

Mumbai: 9.61% prevalence.
Hyderabad: 8.88% prevalence.
Goa: 7.04% prevalence.

National Prevalence:
Overall Prevalence: Approximately 10.95% of the adult Indian population suffers from hypothyroidism.
Gender Disparity: Women are more affected (15.86%) than men (5.02%).
Age Factor: Prevalence increases with age, particularly above 35 years.

Key Factors
Iodine Deficiency: Historically a major cause, though India has implemented salt iodization programs.
Autoimmunity: Anti-TPO antibodies detected in 21.85% of patients indicate autoimmune thyroiditis.
Subclinical Hypothyroidism: Affects 8.02% of the population.
These statistics highlight the importance of awareness and screening for hypothyroidism, especially among high-risk groups like women and older adults.

5. CAUSES

Clinical causes

- Graves' disease (most common):
- Auto immune stimulation of TSH receptors by
- Thyroid adenoma
- Excessive iodine intake
- Thyroiditis (transient release of hormones)
- Hashimoto's thyroiditis (auto immune destruction)
- Iodine deficiency
- Post-thyroidectomy or radioactive iodine therapy
- Pituitary dysfunction (TSH)
- Congenital hypothyroidism
- Thyroid surgery
- Radiation therapy
- Pituitary gland problems
- Grave's disease
- Toxic multinodular goiter
- Thyroiditis
- Pituitary gland problems

Common causes

- Hormonal imbalances
- Ovulation disorders
- Polycystic ovary syndrome

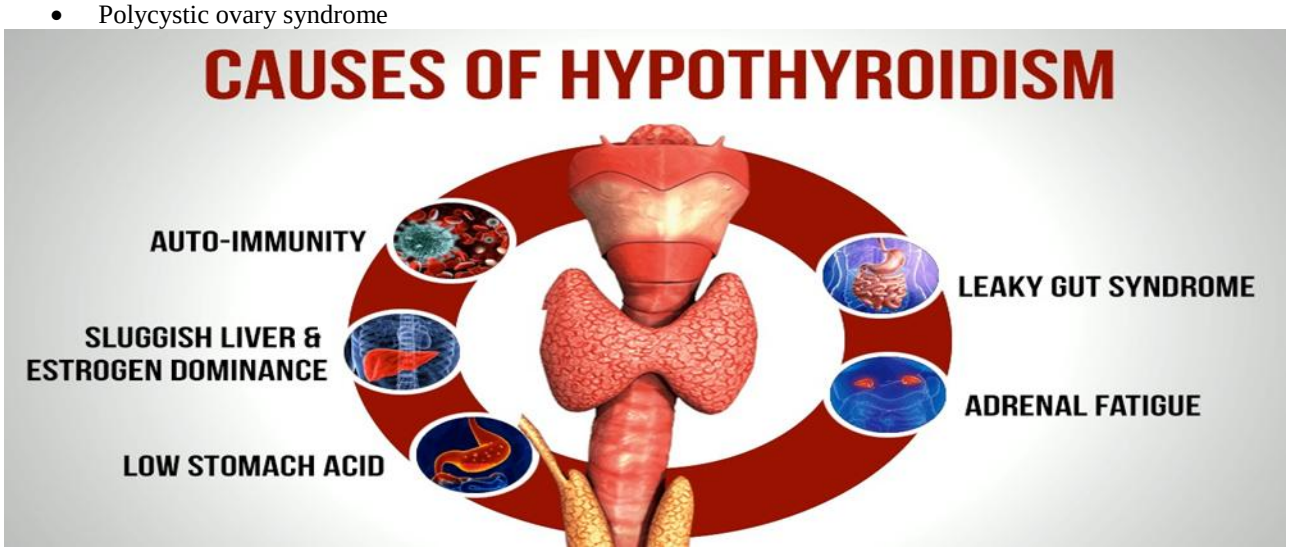


Fig no.1

6. SIGNS ANDS SYMPTOMS

- Fatigue and weakness
- Weight gain
- Cold intolerance
- Hair loss
- Constipation
- Depression
- Muscle aches and stiffness

Clinical symptoms

- Memory problems
- Weight loss
- Anxiety and irritability
- Heat intolerance

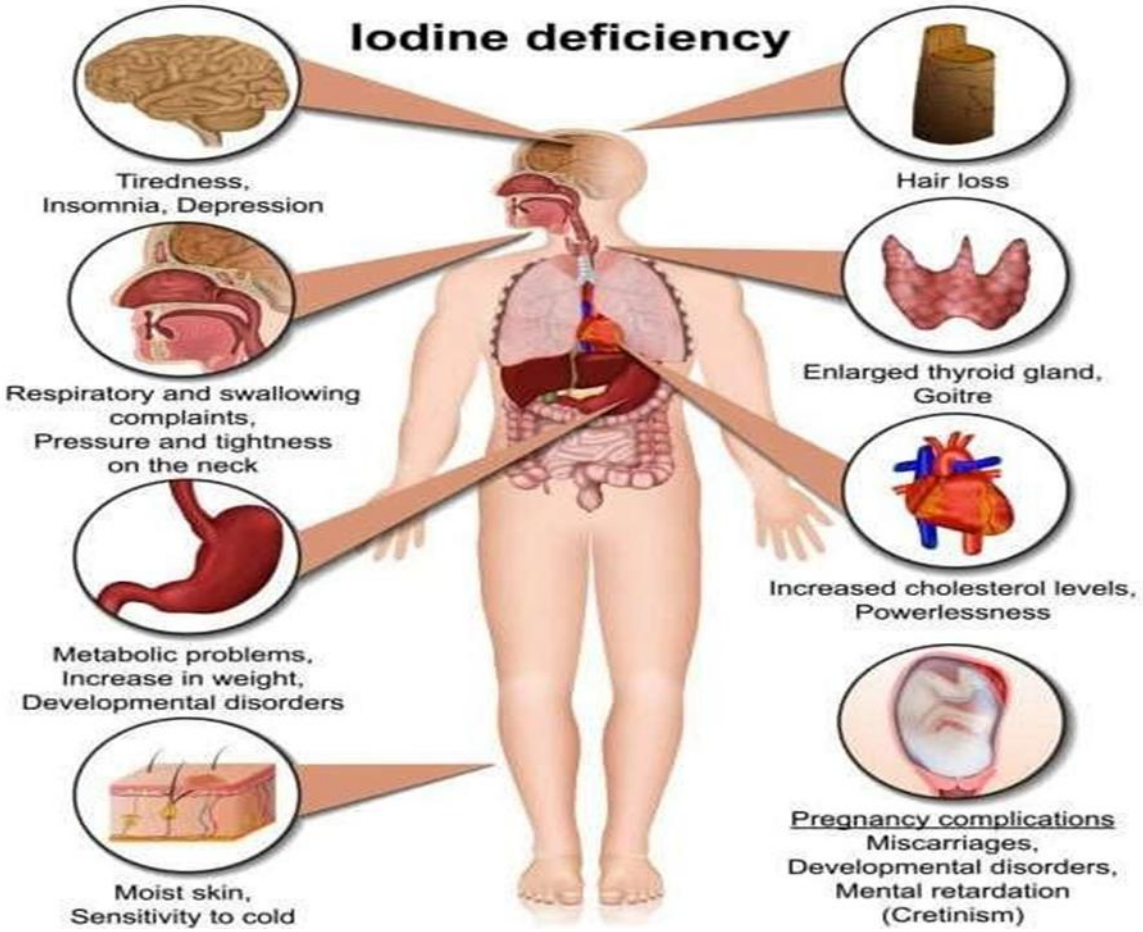
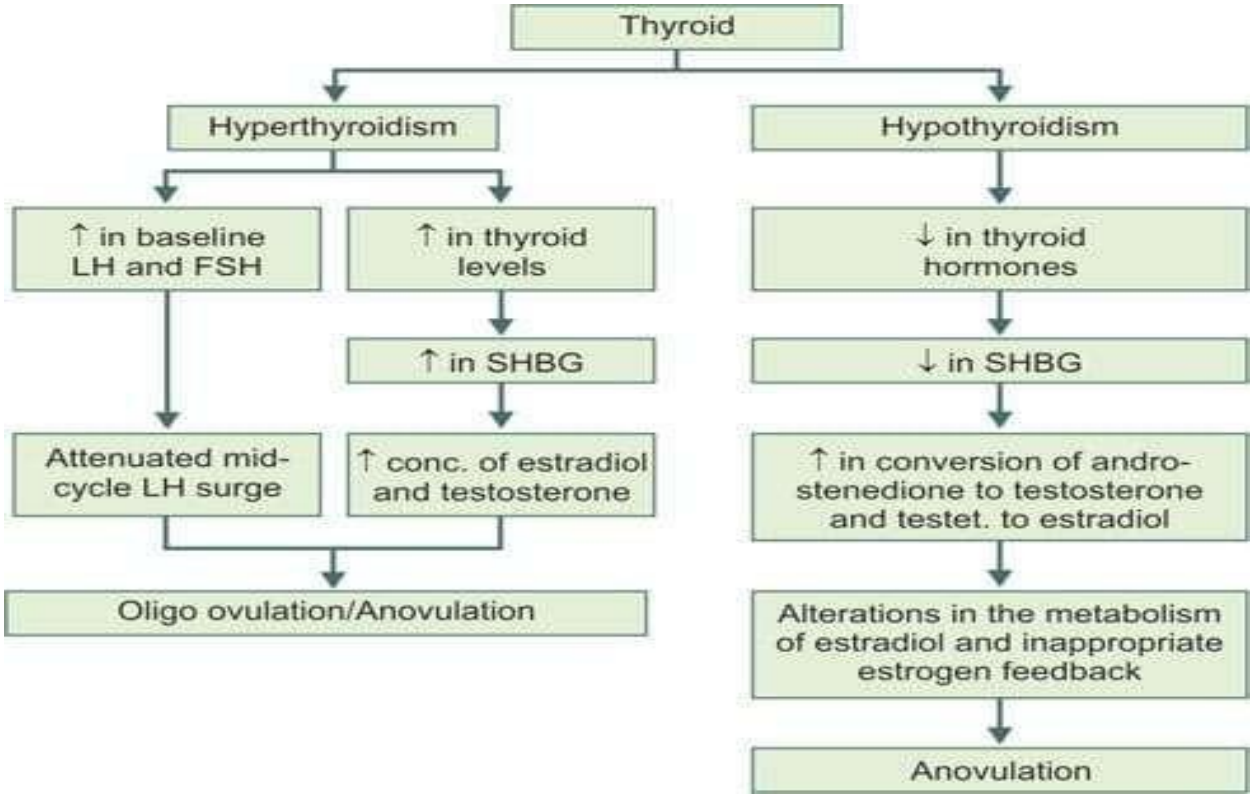


Fig no.2

7. MECHANISM OF ACTION



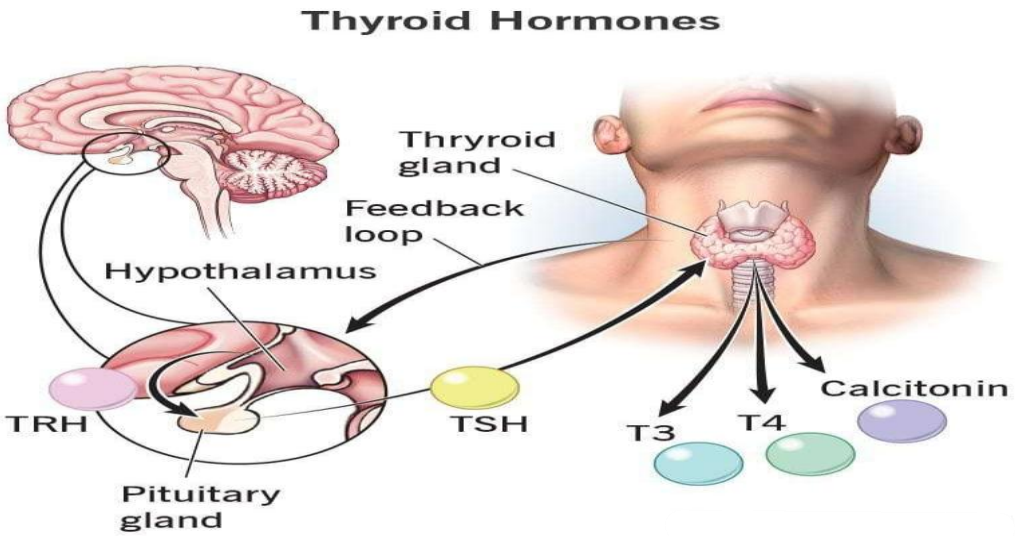


Fig-3

8. PATHOPHYSIOLOGY

- Overproduction or release of T3/T4
- These hormones increase basal metabolic rate (BMR)
- Negative feedback reduces TSH, but in cases like Graves' disease, the thyroid is stimulated independently of TSH.
- Leads to sympathetic nervous system activation and increased beta-adrenergic receptor sensitivity.
- Reduced levels of T3/T4 → slows metabolic processes
- The anterior pituitary increases TSH to stimulate the thyroid (except in secondary causes).
- In autoimmune cases, thyroid peroxidase (TPO) antibodies destroy thyroid tissue.

Clinical effects:

- Tachycardia, palpitations
- Weight loss despite normal/increased appetite
- Heat intolerance, sweating
- Tremors, anxiety
- Goiter (enlarged thyroid)
- Exophthalmos (in Graves' disease)
- Fatigue, lethargy
- Cold intolerance
- Weight gain
- Bradycardia
- Dry skin, constipation
- Depression, slowed thinking
- Myxedema in severe cases

9. DRUG CLASSFICATION

1. Levothyroxine (T4): Synthetic thyroid hormone replacement.
2. Liothyronine (T3): Synthetic triiodothyronine, sometimes used in
3. combination with levothyroxine.
4. Methimazole (Tapazole): Antithyroid medication that reduces thyroid
5. hormone production.
6. Propylthiouracil (PTU): Antithyroid medication, often used in pregnancy.
7. Radioactive iodine: Destroys part of the thyroid gland to reduce hormone production.
8. Beta blockers (e.g., propranolol): Manage symptoms like rapid heartbeat and tremors.
9. Infertility (Related to Thyroid Disorders)1. Clomiphene citrate (Clomid): Stimulates ovulation.
10. Letrozole (Femara): Aromatase inhibitor that stimulates ovulation.
11. Gonadotropins (e.g., FSH, LH): Stimulate ovulation and sperm production.
12. Thyroid hormone replacement: For individuals with hypothyroidism, to regulate thyroid hormone levels and improve fertility.

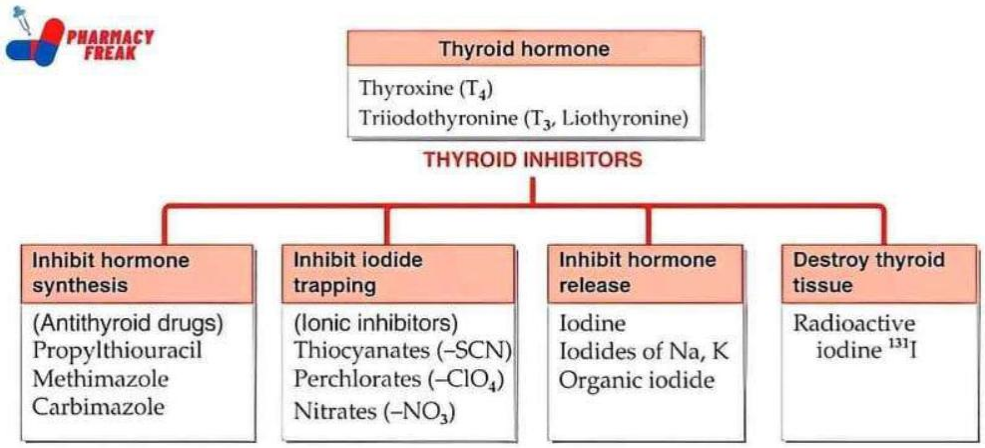


Fig-4

10. TREATMENT ALGORITHM

1. **Diagnosis: TSH, free T4, and free T3 tests.**
2. **Treatment:**
   - Levothyroxine (T4): Synthetic thyroid hormone replacement.
   - Dose adjustment: Based on TSH levels.
   - Medications: Methimazole (Tapazole) or propylthiouracil (PTU).
   - Radioactive iodine: Destroys part of the thyroid gland.
   - Surgery: Thyroidectomy.
   - Thyroid hormone replacement: For hypothyroidism.
   - Antithyroid medications: For hyperthyroidism.
   - Fertility treatments: Clomiphene citrate, gonadotropins, or ART (IVF, ICSI).

3. **Monitoring: Regular TSH tests to ensure proper dosing.**

Hyperthyroidism1. Diagnosis: TSH, free T4, and free T3 tests, thyroid antibodies.
Infertility (Related to Thyroid Disorders)1. Diagnosis: Thyroid function tests (TSH, free T4, free T3).
Monitoring: Regular thyroid function tests and fertility evaluations levothyroxine at a full dose based on body weight (1.6 µg/kg/day) is safe, effective, and requires fewer resources than using a more traditional approach of starting with a small dose and gradually titrating upward.
Levothyroxine Sodium is through its conversion to triiodothyronine (T3), the more active form of thyroid hormone.
Levothyroxine is converted in the body (especially in the liver and kidneys) to the active form triiodothyronine (T3).
T3 binds to nuclear thyroid receptors and regulates gene expression, increasing metabolism, protein synthesis, growth, and development.
Levothyroxine should be taken once per day, 30 to 60 minutes before eating Some drugs and conditions can affect levothyroxine metabolism and effects, and drug-drug and drug-food interactions can affect levels of levothyroxine
Hypothyroidism therapy is performed with the administration of thyroxine, which is transformed by 80% in peripheral tissues to T3. The daily dose of thyroxine in the initiation of substitution therapy depends on various factors, such as body weight, age, the presence of coronary artery disease and cardiac arrhythmias.
In adults the dose is about 1.8 µg/kg body weight, is higher in neonates and young children (3.8 µg/kg) and lower in the elderly (0.5 µg/kg).
In pregnancy, finally, a larger dose is required (2 µg/kg).
During pregnancy the increase in dose that may be required is 25-47% more than the one before pregnancy and it is observed during the 4th to 6th week.
The elderly or patients with coronary artery disease 25-50 µg are administered daily and the dose is increased by 12.5 or 25 g every 2 weeks.
TSH measurement after the initiation of therapy is performed every 4-6 weeks until TSH becomes normal.

11. EFFECT OF THYROIDISM ON INFERTILITY

Hypothyroidism Impacts on Fertility:

Ovulatory Dysfunction:

- Low thyroid hormone levels can interfere with the normal release of an egg from the ovary, making it harder to conceive.
- Menstrual Irregularities:
  Hypothyroidism can cause irregular periods, including lighter, heavier, or more frequent bleeding.
- Hormonal Imbalances:
  Thyroid hormones are essential for normal reproductive function. Their deficiency can lead to higher prolactin levels and alter sex hormone metabolism, which further impacts ovulation and the luteal phase of the menstrual cycle.
- Increased Risk of Miscarriage:
  Untreated hypothyroidism can increase the risk of miscarriage and other complications during pregnancy.
- Underlying Conditions:
  Some causes of hypothyroidism, particularly autoimmune disorders like autoimmune thyroiditis, can also have a direct impact on fertility.
- Implantation Issues:
  Thyroid hormones are crucial for maintaining a healthy uterine lining. Low hormone levels can interfere with progesterone production, hindering the implantation of the fertilized egg.

- Poor Fetal Development:
  In severe cases, untreated hypothyroidism can lead to premature delivery and developmental issues in the baby.
- Reduced Egg Quality:
  Over time, untreated hypothyroidism can lead to poor egg quality, decreasing the chances of successful implantation.
- Irregular Ovulation:
  The thyroid gland regulates reproductive hormones like estrogen and progesterone. Inadequate thyroid hormone levels can interfere with ovulation, making it difficult to conceive.
- Anovulatory Cycles:
  In some cases, hypothyroidism can lead to menstrual cycles where ovulation does not occur at all, or it can cause delayed ovulation.
- Luteal Phase Defect:
  Insufficient thyroid hormone can also affect the luteal phase, which is the time after egg release. This leads to a deficiency in hormones that support pregnancy.
- Ovulation and menstrual cycle:
  Thyroid hormones are essential for regulating the reproductive hormones estrogen and progesterone. Low thyroid function can disrupt the release of eggs from the ovaries (ovulation), leading to irregular or missed periods. This makes it difficult to predict fertile windows for conception.
- Hormonal imbalances:
  Hypothyroidism can lead to an increase in the hormone prolactin, which can suppress ovulation. It can also cause a luteal phase defect, where the period after ovulation is too short for an embryo to implant successfully.
- Miscarriage and pregnancy risks:
  An untreated or poorly managed thyroid condition increases the risk of miscarriage, premature birth, and developmental issues in the baby.
  Maintaining normal thyroid function is especially critical during early pregnancy for the baby's healthy brain development.
- Impact on fertility treatments:
  Thyroid levels are closely monitored during fertility treatments like IVF, as balanced thyroid function can improve the chances of a successful pregnancy.
  The American Thyroid Association recommends specific TSH levels for pregnant women to minimize risks.

Hyperthyroidism impact on infertility:

Hyperthyroidism can cause male infertility by leading to decreased sperm motility and quality, lower semen volume, and an imbalance in sex hormones like estrogen and testosterone. These effects are usually reversible once the hyperthyroid condition is properly treated by a doctor, often through medication or surgery.

1.Sperm quality: Excess thyroid hormone can lead to the production of abnormal sperm that are less capable of fertilizing an egg.

2.Sperm motility: It can reduce sperm movement, making it difficult for them to reach and fertilize an egg.

3.Semen volume: Hyperthyroidism is associated with a decreased volume of semen.

4.Hormonal imbalance: The condition can cause increased estrogen and decreased testosterone levels, which negatively impacts sperm production.

5.Sexual function: Physical symptoms like anxiety and nervousness can interfere with sexual performance, leading to difficulties with erections and ejaculation.

- Hypothyroidism is a condition in which the serum levels of thyroid hormones are below that necessary to carry out physiological functions in the body.
- Hypothyroidism is related to obesity as an increase in body weight gain is seen in hypothyroid patients. Moreover, an inverse correlation between free thyroxine values and body mass index has been reported.
- Leptin, a polypeptide hormone produced by adipocytes, was originally thought to be an antiobesity hormone due its anorexic effects on hypothalamic appetite regulation. However, nowadays it is known that leptin conveys information about the nutritional status to the brain being considered a crucial endocrine factor for regulating several physiological processes including reproduction.
- Since the identification of thyroid hormone and leptin receptors on the testes, these hormones are being recognized as having important roles in male reproductive functions.
- A clear link exists among thyroid hormones, leptin and reproduction. Both hormones can negatively affect spermatogenesis and consequently may cause male infertility.

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