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Exploring Thyroid Disease In Pregnancy: Advancement In Diagnosis And Clinical Strategies.

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❖ **Abstract:**

Thyroid dysfunction during pregnancy poses a significant challenge in clinical practice, necessitating refined diagnostic approaches and tailored management strategies. This abstract explores emerging insights into thyroid disease during pregnancy, focusing on the complexities of diagnosis and the evolving landscape of clinical management. Recent research highlights the intricate interplay between maternal thyroid function and fetal neurodevelopment, emphasizing the critical importance of early detection and intervention. Additionally, advancements in diagnostic modalities, such as novel biomarkers and imaging techniques, offer enhanced precision in identifying thyroid dysfunction throughout pregnancy. Moreover, the evolving understanding of the immunological and genetic factors contributing to thyroid disorders in pregnancy underscores the need for personalized therapeutic approaches.

This abstract also delvesinto the expanding repertoire of therapeutic options, including pharmacological interventions and lifestyle modifications, aimed at optimizing maternal and fetal outcomes. Furthermore, interdisciplinary collaboration between endocrinologists, obstetricians, and neonatologists is imperative for comprehensive care delivery. By synthesizing these novel perspectives, this abstract advocates for a paradigm shift in the approach to thyroid disease in pregnancy, fostering improved maternal and neonatal health outcomes through integrated diagnostic and therapeutic strategies.Overt thyroid disease is associated with a wide range of adverse obstetric and child development outcomes. An increasing number of studies now indicate that milder forms of thyroid dysfunction are also associated with these adverse pregnancy outcomes.

Keywords: Pregnancy,Hyperthyroidism,Hypothyroidism,Thyroiditis,Graves disease,Autoimmune Disorder,Therapeutic Approach,Thyroid Disease.

Introduction:

Thyroid hormone is vital for common the pregnancy and the development of the fetus. In the first fifty percent of pregnancy, placental and newborn development depend on the offer of maternal thyroid hormone. As a consequence, neglected maternal hypothyroidism is associated with a greater likelihood of problems with pregnancy, as well as negative impacts for the child(1).Pregnancy is linked that have significant but reversible modifications to maternal thyroid physiological processes that may result to confusion in the diagnosis of thyroid irregularities.Initially, there exists a moderate enlargement of the thyroid gland due to the effects of pregnancy hormones, which induce hyperplasia of the glandular tissue and an increase in blood vessel formation. The ultrasound assessment of the thyroid gland in pregnancy reveals a rise in size, while its echogenicity remains consistent (2). Research on thyroid dysfunction during pregnancy has significantly grown in the last ten years. This surge in interest can be attributed to two studies published in 1999, which indicated that children born to mothers with hypothyroidism, whether overt or subclinical, are more likely to experience impaired neurodevelopment(3). The reason behind the regular screening of expectant mothers relies on the documented occurrence of subclinical hypothyroidism and the possible advantages of treatment while pregnant. It is crucial to note that most women who would be detected through widespread screening during pregnancy in the United States would have subclinical hypothyroidism(4).

Thyroid disorders can have a significant impact on both the mother and the developing fetus during pregnancy. The thyroid gland, situated in the neck, produces hormones that play a crucial role in regulating metabolism and other essential bodily functions. Disruption in thyroid function during pregnancy can result in various complications. Thyroid disease is one of the most common endocrine disorders in pregnancy globally, second only to hyperglycemia. Hypothyroidism is more prevalent, affecting women in regions with both sufficient and insufficient iodine levels. In iodine-sufficient areas, autoimmune thyroid disease is the primary cause of overt hypothyroidism, with detectable thyroid antibodies in up to 60% of pregnant women with elevated TSH levels. The management of subclinical hypothyroidism (SCH) remains a topic of debate due to inconsistent research findings. Hyperthyroidism caused by Grave's disease (GD) affects approximately 0.2%–0.4% of pregnant women, followed by gestational hyperthyroidism and toxic adenomas (5).

Additional significant factors that impact thyroid function include various physiological changes that occur during pregnancy. These alterations in maternal thyroid homeostasis can collectively contribute to gradual enhancements in the production of thyroid hormones. The maternal glomerular filtration rate is heightened due to an increase in cardiac output, leading to elevated renal clearance and excretion of iodide(6). Maternal thyroid function returns to its normal activity within 6 months after delivery, unless there is a development of thyroid dysfunction(7).Drug use during pregnancy is widespread, yet numerous women remain hesitant about taking medications while pregnant. There is a tendency to overestimate the risks of birth defects and to refrain from using any medication as soon as pregnancy is confirmed(8).

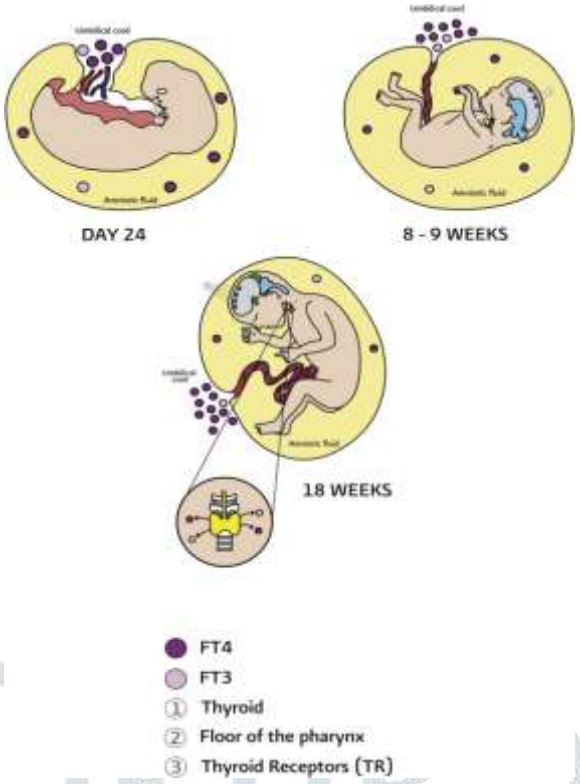

Fig no 1: Development of Thyroid gland on the 24th day of gestation.

Pathophysiology:

Throughout pregnancy, elevated levels of thyroid hormones are essential to facilitate the required physiological adjustments in maternal cardiac output, blood volume, fat reserves, cholesterol metabolism, and the production of pituitary hormones. Moreover, during the initial 10-12 weeks of pregnancy, the developing embryo/fetus relies on maternal thyroid hormone for metabolic processes, particularly crucial for axonal growth, myelination, and cellular differentiation in the brain and central nervous system until its own thyroid gland becomes functional(CNS)(9). Insufficient levels of thyroid hormone can impact various bodily systems, leading to negative effects on pregnancy and hindering the proper growth of the fetal nervous system. Although the most severe consequences are seen in cases of overt hypothyroidism in mothers, even minor deficiencies in thyroid hormone during crucial stages of fetal development can have long-term consequences(10).

A comprehensive list of factors that can lead to severe hypothyroidism includes iodine deficiency, autoimmune disease, thyroidectomy, radioablative therapy like radioactive iodine (RAI), and abnormalities within the hypothalamus or pituitary gland. Prior to pregnancy, many women are already aware of this condition. For women who do not have preexisting hypothyroidism, the additional strain on the thyroid gland during pregnancy can expose any underlying thyroid issues. Pregnancy has even been likened to a stress test for the thyroid gland by some(11). Hypothyroidism may impact fertility, but 11% of women with overt hypothyroidism can conceive without needing thyroid hormone replacement. Prior to the development of the fetal thyroid gland, the fetus relies on maternal thyroid hormone production to meet its needs(12).

The function, synthesis, and secretion of thyroid hormones rely on the coordination and functioning of various developmental processes. Dysfunction may manifest at any point during this process. The thyroid gland must go through cell migration, differentiation, and maturation. The proper development of the

hypothalamic-pituitary-thyroid axis is essential, along with the maturation of the thyroid gland, in order to ensure the production of functional thyroid hormones from a systemic-endocrine perspective(13). The fetal thyroid gland reaches maturity at around 11-12 weeks of gestation, however, the production of functional thyroid hormone does not commence until the middle of the second trimester, specifically around 16-17 weeks of gestation(14). During the initial trimester, the fetal central nervous system (CNS) undergoes crucial development, making it imperative to have a sufficient supply of maternal thyroid hormone(15). Maternal hypothyroidism during pregnancy is characterized by an increased TSH level, excluding rare conditions like TSH-secreting pituitary tumors, thyroid hormone resistance, and certain cases of central hypothyroidism with biologically inactive TSH(16).

It is crucial to distinguish between transient gestational hyperthyroidism and thyrotoxicosis caused by intrinsic thyroid disease, particularly Grave's hyperthyroidism. This necessitates a thorough assessment and examination. Untreated overt hyperthyroidism caused by GD poses a substantial threat to both maternal and fetal health. Patients with a positive family history of thyroid disease, significant thyroid enlargement, or eye findings indicative of thyroid-related orbitopathy like proptosis should undergo a complete thyroid function panel including Thyroid Stimulating Hormone (TSH), Thyroid Hormone (TH), and Thyrotropin Receptor Antibodies (TRAB)(17).

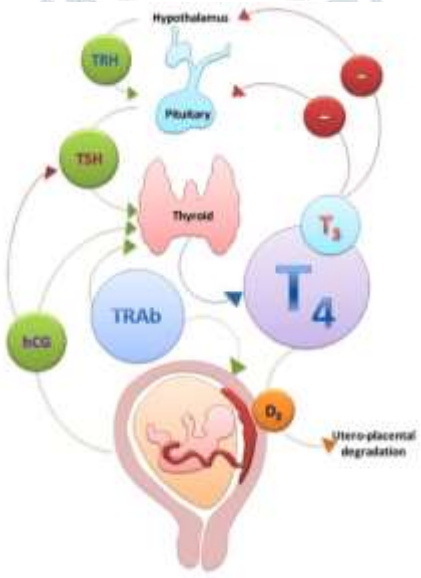

Fig no 2: Hypothalamic pituitory thyroid axis and Pregnancy.

- **Fetal goiter:**

Goiters are the clinical presentation of thyroid gland dysfunction in the fetus. The prevalence of fetal thyroid goiter is estimated to range from 1 in 30,000 to 1 in 50,000 live births (18). There exist two categories of Thyroid Receptor Antibodies (TRAbs), namely Thyroid stimulating antibody (TSAb) and Thyroid Stimulating Blocking Antibody (TSBAb). TSAb leads to hyperthyroidism, while TSBAb leads to hypothyroidism. It is worth noting that TSBAb has a lower probability of causing fetal thyroid goiters(19). The mechanical (mass effect) and biochemical consequences of fetal thyroid goiters are widely acknowledged. Possible complications that may arise due to the overall size and position of the mass include rare occurrences of esophageal and tracheal compression, leading to polyhydramnios or asphyxia. Additionally, dystocia

during delivery is also a potential concern. The biochemical consequences of thyroid goiters vary based on the cause of the goiter. In instances of hyperthyroidism, one may experience cardiac failure, growth restriction, and mental retardation. Delayed motor and mental milestones, along with deafness, are observed in cases of hypothyroidism. Further elaboration on these aspects will be provided subsequently. Fetal thyroid goiters are typically identified through ultrasonography. It is most effectively accomplished during the second or third trimester. Expectant mothers with documented thyroid disorders should undergo thorough screening. Diagnostic nomograms utilizing gestational age have been created to assist in the diagnosis(20).

- **Hypothyroidism:**

Hypothyroidism is a medical condition distinguished by inadequate production of thyroid hormones by the thyroid gland (primary), due to a decrease in pituitary function (secondary), or a decrease in hypothalamic stimulation (tertiary). Thyroid hormone deficiency may present as moderate or severe, known as overt or clinical hypothyroidism, characterized by elevated TSH levels beyond the upper limit of normal and decreased FT4 levels below the reference range(21). Subclinical hypothyroidism occurs when the TSH levels exceed the upper limit of normal, while the FT4 levels remain within the reference rangeIsolated hypothyroxinemia is characterized by a maternal TSH level within the normal range, while the FT4 concentration falls below the reference range (22). In relation to isolated hypothyroxinemia, the prevalence has been documented to be around 1.3% among pregnant women, although it can reach as high as 25.4%(23)

Chronic autoimmune thyroiditis is the prevailing cause of primary hypothyroidism during pregnancy (Hashimoto's thyroiditis) It is a painless inflammation resulting in the gradual enlargement of the thyroid gland, marked by diffuse lymphocytic infiltration, fibrosis, parenchymal atrophy, and eosinophilic change. Additional significant factors contributing to primary hypothyroidism are endemic iodine deficiency and a past medical history involving ablative radioiodine therapy or thyroidectomy. Secondary hypothyroidism originates from the pituitary gland. For instance, Sheehan's syndrome, resulting from a past obstetric hemorrhage, is defined by pituitary ischemia and necrosis leading to deficiencies in one or more pituitary hormones. Additional factors leading to secondary hypothyroidism consist of lymphocytic hypophysitis and a past hypophysectomy. Tertiary hypothyroidism, also known as hypothalamic hypothyroidism, is an uncommon condition. Central hypothyroidism is characterized by insufficient activation of the thyroid gland due to a malfunction at the pituitary or hypothalamic level. Women diagnosed with clinical hypothyroidism face a higher likelihood of experiencing pregnancy complications, including early pregnancy loss, preeclampsia, placental abruption, low birth weight, and stillbirth. Improved pregnancy outcomes have been linked to the treatment of women diagnosed with overt hypothyroidism(24). Overt hypothyroidism occurs in approximately 1 out of every 1,000 to 3 out of every 1,000 pregnancies. It is characterized by nonspecific and vague signs or symptoms that can be easily mistaken for common pregnancy-related complaints. The onset of these symptoms is often gradual and subtle. The initial signs encompass weariness, bowel irregularity, sensitivity to cold, and muscular spasms. Insomnia, weight gain, carpal tunnel syndrome, hair loss, voice changes, and intellectual slowness are potential symptoms that can develop. Women who indicate that these symptoms have deteriorated in the past year are at a higher risk of having evident thyroid disorder(25).

Upon confirmation of hypothyroidism, it is recommended to initiate treatment with L-thyroxine replacement therapy. Adults with hypothyroidism need around 1.7 micrograms per kilogram of body weight per day for complete replacement, although elderly individuals may need a lower dosage(26). As a result of heightened metabolic demands during pregnancy, the thyroid function test outcomes for pregnant women who are in good health vary from those of nonpregnant women who are also in good health. In 2012, the ATA put forth pregnancy-specific reference intervals for TSH (Thyroid Stimulating Hormone) and FT4 (Free Thyroxine), ideally tailored to each trimester (27). In countries across the globe, iodine deficiency stands as the prevailing factor behind hypothyroidism. Nevertheless, in nations where iodine levels are sufficient, such as the United States, the primary cause shifts to autoimmune thyroiditis or Hashimoto's thyroiditis(28).On the other hand, other risk factors for the development of hypothyroidism during pregnancy have now been defined in Fig no 3.

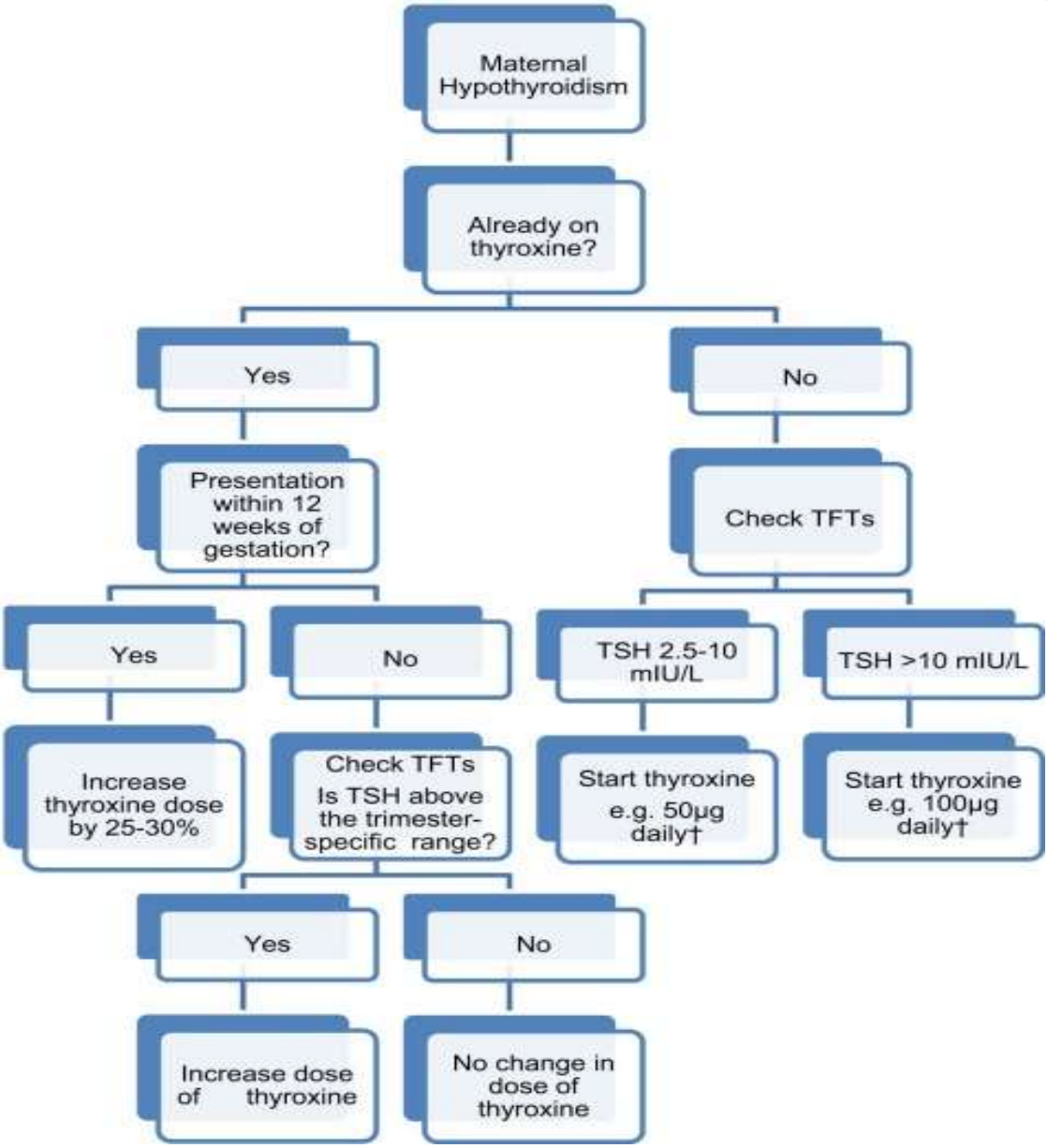

Fig no 3: Treatment of maternal hypothyroidism in pregnancy thyroid function tests(TFTs),Thyroid stimulating Harmone(TSH).These are conservative estimates based on our experience.Higher doses may be required and depending on the patient total body weight.

- **Hyperthyroidism:**

During pregnancy, there are two primary subtypes of overt hyperthyroidism that may manifest. The first subtype is a pathological variation that primarily impacts women with Graves disease or other conditions characterized by autonomous thyroid hormone production, such as multinodular toxic goitre or toxic adenomasPathological hyperthyroidism in pregnancy is uncommon, with prevalence rates in Western nations ranging from 0.5% to 1.3% for pre-existing Graves disease, 0.05% for new-onset Graves disease, and 0.1% for autonomous thyroid hormone production (29). The condition frequently manifests with evident biochemical irregularities (low TSH levels along with elevated free T4 levels usually exceeding 1.5 times the upper normal limit), clinical signs like rapid heartbeat, shaking, or nervousness, and is linked to an increased likelihood of negative pregnancy results. The alternative form is distinguished by temporary increases in thyroid activity caused by elevated hCG levels, which usually reach their highest point around the 10th week of pregnancy. (FIG. 1). Gestational hyperthyroidism is diagnosed in 0.3–1.0% of pregnant women based on population-based reference ranges, specifically a TSH concentration below the 2.5th percentile and a free T4 concentration exceeding the 97.5th percentile(30).

A low or unnoticeable TSH level in pregnancy, particularly in the initial trimester, is typically caused by hCG directly stimulating the thyroid gland, leading to temporary gestational thyrotoxicosis. The same effect can be produced by hyperemesis gravidarum, hydatidiform mole, choriocarcinoma, and multiple pregnancies(31). Graves' disease is the primary reason for hyperthyroidism, as it involves an autoimmune-driven activation of the thyrotropin receptor. Additional causes of hyperthyroidism consist of toxic multinodular goiter, toxic adenoma, and thyroiditis.Traditionally, individuals with hyperthyroidism commonly experience signs such as sensitivity to heat, excessive sweating, rapid heartbeat, shortness of breath during physical activity, increased hunger, frequent bowel movements, loss of weight, tremors, and irregular menstrual cycles. Classic symptoms may not manifest in all patients. Particularly in elderly patients, atypical symptoms such as fatigue, weight gain, and constipation are more commonly observed. Physical examination may reveal notable signs such as an increased pulse pressure, tachycardia, warm skin, stare and eyelid retraction, enlarged thyroid, and tremor. Specific diagnoses are linked to particular findings. For instance, Graves' disease may be indicated by a thyroid that is diffusely enlarged with a bruit or pyramidal lobe, the existence of pretibial myxedema, and ophthalmologic signs of heightened retroorbital pressure such as conjunctival injection, exophthalmos, and extraocular muscle involvementA toxic multinodular goiter may be indicated by a large multinodular goiter along with a background of gradually worsening thyrotoxic symptoms. In cases where hyperthyroidism is suspected, it is essential to verify the diagnosis through thyroid function tests. A high free T4 level coupled with a TSH level that cannot be detected is indicative of hyperthyroidism. Certain individuals diagnosed with Graves' disease may experience toxicosis, characterized by an increased T3 hormone, a normal free T4 hormone, and a decreased TSH level. Consequently, for patients exhibiting clinical hyperthyroidism with an undetectable TSH and a normal free T4 level, it is advisable to assess the T3 hormone. Some patients may exhibit a low TSH level alongside normal free T4 and T levels, indicating subclinical hyperthyroidism. In certain cases, the TSH level may be inappropriately normal or slightly elevated in patients with clinical

hyperthyroidism and elevated free T4 and T levels. Within this group of individuals, it is important to consider the uncommon occurrence of a TSH-secreting pituitary adenoma or thyroid hormone resistance(32).

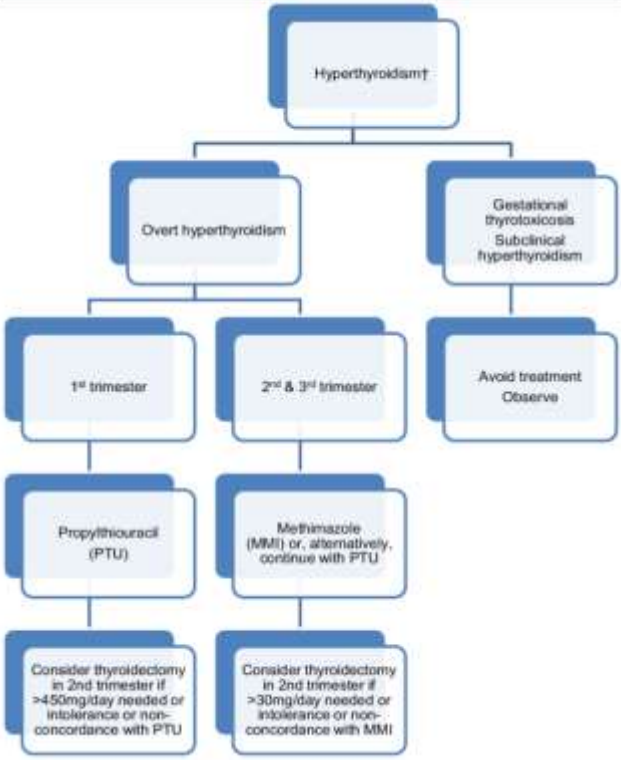

Fig no 4: Treatment of hyperthroidism in maternal throid disease in pregnancy.

- **Graves Disease:**

Graves' disease is the primary factor leading to hyperthyroidism in expectant mothers, commonly observed in pregnant women(33). As previously mentioned, Graves' disease is distinguished by the presence of goiter, occasionally accompanied by a bruit, an elevated T-to-T4 ratio, and sometimes ophthalmopathy. The immune response is typically suppressed during pregnancy, leading to an improvement in Graves' disease as the duration of pregnancy progresses. Patients who have hyperthyroidism should receive treatment during the early stages of pregnancy. If the condition improves as the pregnancy progresses, the dosage of medications can be gradually reduced. Increased fetal and maternal morbidity has been linked to a delay in receiving treatment. Thionamides or surgery are the only available treatment options, as radio active iodine (RAI) ablation is not recommended during pregnancy(34). Propylthiouracil (PTU) is the recommended medication for managing Graves disease in pregnant women. The objective of treatment is to keep the free T4 levels within the high-normal range, while ensuring that TSH remains undetectable. Pregnant women can generally handle mild hyperthyroidism quite well, and by maintaining a high-normal free T index, they can require a lower dosage of PTU for maternal treatment. Graves' disease has the potential to improve during pregnancy, allowing for the management of hyperthyroidism with minimal PTU doses, and in certain situations, discontinuation of the medication may be possible. At times, there may be a worsening of Graves' disease after childbirth. Hence, it is crucial to regularly monitor thyroid tests during pregnancy and immediately after giving birth in order to make necessary adjustments in PTU dosage (35).

As mentioned earlier, PTU has the ability to pass through the placenta, which means it can potentially hinder the production of thyroid hormones in the fetus. It has been observed that around 10% of infants born to women who take PTU may develop neonatal goiter, with or without hypothyroidism. The likelihood of neonatal goiter may vary depending on the dosage of PTU(36). Hence, it is not advisable to combine PTU and L-thyroxine as it leads to the administration of excessive PTU doses in combination therapy. Long-term studies indicate that there are no adverse effects (such as intellectual impairment or other issues) following exposure to thionamides(37). Surgery can be considered as an option instead of thionamides for managing Graves' disease during pregnancy. Patients with hyperthyroidism must be medically managed with thionamides and supplemented with iodides for 10 days prior to undergoing surgery. Despite the fact that myocardial infarction (MI) and iodides are typically contraindicated during pregnancy, short-term iodide administration for thyroid surgery preparation has been utilized successfully without any issues. Surgery on the thyroid gland is typically only considered for individuals with severe thyrotoxicosis or those who are unable to tolerate thionamides, and is usually done after the first trimester (38). The utilization of P-blockers, like propranolol, in pregnancy remains a topic of debate. Expectant women with hypertension who are administered P-blockers during pregnancy have experienced issues such as placental insufficiency, intrauterine growth retardation, neonatal hypoglycemia, and bradycardia. It is unclear whether these complications are a result of maternal hypertension or the use of blockade. Other research studies indicate that pregnant women can safely receive treatment with P-blocking drugs and, in fact, show better fetal outcomes in hypertensive mothers treated with P-blockers compared to methyldopa or hydralazine (39).

❖ **Treatments:**

➢ **Hypothyroidism**:

It is recommended to address hypothyroidism prior to conception for optimal outcomes. Levothyroxine is the preferred treatment option, aiming for a TSH level below 2·5 mIU/L in women who are planning to conceive(40). Levothyroxine demands escalate starting from the fifth week of pregnancy and reach a stable level by the twentieth week;(41) Consequently, for women previously diagnosed with hypothyroidism, it is essential to monitor serum TSH levels and adjust the levothyroxine dosage promptly upon confirmation of pregnancy. A retrospective study revealed that only 17% of hypothyroid women with preconception serum TSH levels below 1·2 mIU/L needed to increase their levothyroxine dosage during pregnancy, while 50% of those with preconception serum TSH levels between 1·2–2·4 mIU/L required a dosage adjustment. Failure to modify the levothyroxine dosage appropriately can lead to worsening maternal hypothyroidism due to the heightened demand for thyroid hormone during pregnancy(42).

To ensure the normalization of thyroid function in pregnant women diagnosed with overt hypothyroidism, it is crucial to promptly adjust the levothyroxine dose. The aim is to achieve and sustain serum TSH concentrations within trimester-specific TSH reference ranges. Following the start of treatment, it is recommended to reevaluate thyroid function within a period of 30 to 40 days, and subsequently every 4 to 6 weeks. During pregnancy, the dosage of levothyroxine should be modified accordingly based on serum TSH

levels(43,44). The diagnosis of primary hypothyroidism is easily confirmed by an elevated serum TSH concentration. The detection of thyroid antibodies further supports this diagnosis. Based on certain research, a serum TSH level exceeding 2.5 mU/l in women who are not pregnant should be considered as an indicator of thyroid dysfunction. Likewise, a TSH level greater than 2.5 mU/l is considered excessively high during the initial trimester of pregnancy(46). If the serum TSH level is greater than 4 mU/l, regardless of whether thyroid antibodies are present or not, it is conclusive evidence of thyroid hypofunction.

- **Hyperthyroidism:**

Biochemical support for the diagnosis of hyperthyroidism can be obtained when extremely low levels of TSH are detected (< 0.1 mU/l), along with elevated T4 concentrations. Nevertheless, it is important to note that approximately 10-20% of pregnant women may exhibit low plasma TSH levels without experiencing any symptoms of thyrotoxicosis (47).. Half of these women exhibit detectable yet below-normal levels of serum TSH, while the remaining half showcases completely suppressed concentrations(48). A trend in the T4 serum concentration can provide valuable assistance in distinguishing between temporary physiological states and thyrotoxic conditions when TSH levels are low(49). Therefore, a comprehensive diagnosis requires more than just biochemistry. Factors such as TSH receptor antibodies, eye disease, family history, goiter, weight loss, arrhythmias, and other considerations must also be taken into account.

- **Grave's Disease:**

1. ATDs: The cornerstone of medical treatment consists of the antithyroid drugs (ATDs) MMI, PTU, and carbimazole. These medications have the ability to pass through the placenta, posing potential risks to both the mother and the fetus. Therefore, in certain cases, careful monitoring of thyroid function may be preferred over the administration of medical management. In certain countries, carbimazole is utilized as an alternative to MMI or PTU, as it is rapidly converted to MMI after being absorbed. The conversion rate is 10mg of carbimazole for every 6mg of PTU(50). ATDs can lead to maternal side effects in approximately 3% to 5% of women undergoing treatment. The most frequently observed side effect is a rash, while more uncommon but severe side effects encompass agranulocytosis (0.15%) and liver failure (< 0.1%). These side effects typically manifest during the commencement or resumption of treatment(51).

2. Treatment targets: It is recommended to utilize the minimal effective amount of ATD in order to keep the FT4 levels near the upper limit of normal and the TT4 levels at 1.5 times the upper limit of the nonpregnant reference range(52,50,54). It is possible for TSH levels to stay low even after T4 levels have returned to normal, so TSH should not be the main focus when determining treatment effectiveness. If TSH levels change from undetectable to detectable, the dose of anti-thyroid drugs should be reduced.
3. Radioactive iodine: RAI should not be used during pregnancy or by lactating mothers. It is standard procedure to conduct a pregnancy test before administering RAI. However, if a fetus is accidentally exposed to RAI, the gestational age plays a crucial role in determining the potential impact. Before the 10–12th week, the fetal thyroid does not absorb RAI, so there should be no anticipation of fetal thyroid dysfunction or negative consequences. However, once the fetus reaches 12 weeks of age, RAI will be absorbed by the fetal thyroid, leading to destructive effects.(54). Adverse consequences resulting from fetal thyroid destruction, prenatal

hypothyroidism, and consequent neural impairment may occur in this scenario. The administration of RAI to women postpartum is addressed in the section concerning the monitoring and management of postpartum GD.

4. Surgical Management: There exist a restricted range of circumstances in which a thyroidectomy ought to be employed for managing GD while pregnant. These circumstances encompass patients who possess allergies or contraindications to MMI or PTU, patients who do not comply with ATDs, or patients for whom attaining a euthyroid state with ATD is unattainable. If necessary, the surgical procedure should be performed during the second trimester. Surgical readiness can be achieved by utilizing beta-blockade and high-dose iodine, specifically through the use of a saturated solution of potassium iodide (SSKI). Furthermore, the administration of cholestyramine can be employed to reduce the enterohepatic circulation of TH, while systemic glucocorticoids aid in diminishing the conversion of T4 to T3. Plasmapheresis has proven to be an effective treatment in pregnancy for severe cases of hyperthyroidism and in situations involving agranulocytosis (55,56).

❖ **Classification of Anti-thyroid drugs:**

A. Inhibit hormone synthesis (Antithyroid drugs)-Propylthiouracil,Methimazole,Carbimazole.
B. Inhibit Iodide trapping(ionic inhibitors)-Thiocyanates(-SCN),Perchlorates(-ClO_4),Nitrates(-NO_3).
C. Inhibit hormone release-Iodine,Iodides of Na and K, Organic iodide.
D. Destroy thyroid tissue-Radioactive iodine (I^{131},^{125}I,^{123}I)

❖ **Drugs:**

➢ **Propylthiouracil:** Propylthiouracil exhibits lower potency on a dose-to-dose basis. It is considered a highly potent medication with minimal transfer across the placenta and into breast milk. The plasma half-life (t1/2) is approximately 1-2 hours, and a single dose provides effects for 4-8 hours. Propylthiouracil does not produce active metabolites. Multiple doses (2-3) are required daily for optimal efficacy. Propylthiouracil impedes the conversion of T4 to T3 hormone. Its therapeutic uses involve decreasing thyroid hormone production. The pharmacology of propylthiouracil is mainly concerned with liver toxicity, which is uncommon but more frequently observed in children and pregnant women. It is solely indicated for thyroid storm due to its impact on reducing T4 to T3 conversion, particularly in the initial stages of pregnancy.

➢ **Carbimazole:** Carbimazole is approximately five times more potent than propylthiouracil, with lower protein binding. It crosses the placenta and is excreted in larger amounts in breast milk. The plasma half-life (t1/2) ranges from 6 to 10 hours. A single dose of carbimazole remains effective for 12 to 24 hours. Carbimazole creates an active metabolite akin to methimazole, which is accessible in Europe. Methimazole is valued for its therapeutic properties in decreasing thyroid hormone production, making it a favored option among anti-thyroid medications. Nonetheless, it is advised against using methimazole during the initial trimester of pregnancy due to the potential for embryopathy. Carbimazole is generally prescribed as a once-daily dose and does not impede the conversion of T4 to T3 hormones.

- **Perchloates :** The primary purpose of its therapeutic use is to improve the response to thioamides in refractory Grave disease. This medication is not sold commercially and must be specially prepared.
- **Iodine :** Iodine serves as a building block for thyroid hormones, but paradoxically, it is the quickest acting thyroid inhibitor. In Grave's disease, an enlarged gland may undergo changes such as shrinking, becoming firm, and less vascular. The thyroid function gradually normalizes as hormone release from the gland ceases completely. The thyroid gland shrinks and colloid levels are replenished. The body's reaction to iodine and iodides remains the same, as elemental iodine is converted to iodide in the intestines. After regular administration, the maximum effects are observed within a span of 10-15 days. However, following this period, there is a phenomenon known as 'thyroid escape' which can lead to a resurgence of thyrotoxicosis with even greater intensity. This exacerbation of hyperthyroidism is particularly prominent in cases of multinodular goiter.

- **Radioactive Iodine :** The stable isotope of iodine has an atomic mass of 71. On the other hand, the radioactive isotope of iodine that is used for medicinal purposes is 131 I, which has a physical half-life of 8 days. Despite being radioactive, the chemical behavior of 131 I is similar to that of the stable isotope. Y-rays, which are higher energy X-rays emitted by atomic nuclei, along with B particles, serve different purposes. The former is valuable in tracer studies as they can pass through tissues and be tracked using a counter. On the other hand, the latter is employed for its ability to harm thyroid cells. The thyroid gland concentrates iodine, which is then incorporated into colloid and emits radiation from within the follicles. The beta particles can only penetrate a depth of 0.5-2 mm into the tissue. The follicular cells of the thyroid are affected internally, leading to pyknosis and necrosis, followed by fibrosis when a significant dose is administered, without causing harm to surrounding tissues. By selecting precise doses, partial ablation of the thyroid can be attained. Radioactive iodine, in the form of sodium salt of 131 I dissolved in water, is orally administered(57).

❖ Conclusion:

Early diagnosis and management of thyroid dysfunction in pregnancy is essential to avoid adverse maternal and fetal outcomes. Overt hypothyroidism and hyperthyroidism should be treated appropriately. Thyroid disease during pregnancy is a complex and multifaceted condition that requires careful management and monitoring. From hypothyroidism to hyperthyroidism and thyroid nodules, these disorders can have significant implications for both the mother and the developing fetus. Proper diagnosis, treatment, and follow-up are essential to ensure optimal maternal and fetal outcomes. Collaborative efforts between obstetricians, endocrinologists, and other healthcare providers are crucial in providing comprehensive care for pregnant women with thyroid disease. Further research and guidelines are needed to improve our understanding and management of thyroid disorders in pregnancy, ultimately leading to better outcomes for mothers and their babies. Subclinical hypothyroidism and positive antithyroid antibodies are present in a large number of pregnant women.

❖ **Reference**:

1) Poppe, K. & Glinoer, D. Thyroid function and human reproductive health. Endocr., 702–755 (2010).
2) Rasmussen NG, Hornnes PJ, Ultrasonography determined thyroid size in pregnancy and postpartum: the goitrogenic effect of pregnancy. Am J Obstet Gynecol 1989;16–20.
3) Palomaki GE, Allan WC, Williams JR, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999;49–55.
4) Casey BM, Wells CE, McIntire DD, Byrd W, et al. Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol 2005;39–45.
5) American Thyroid Association. (2017). Thyroid Disease and Pregnancy. Retrieved from https://www.thyroid.org/thyroid-disease-pregnancy.
6) Becker DV, Hollowell JG, et al. Iodine supplementation for pregnancy and lactation-United States and Canada: recommendations of the American Thyroid Association. Thyroid. 2006;49-51.
7) Glinoer D, Lemone M,De Nayer P, et al. Partial reversibility during late postpartum of thyroid abnormalities associated with pregnancy. J Clin Endocrinol Metab. 1992;74:453-7.
8) A.M. van Trigt, F.M. Haaijer-Ruskamp, Questions about drugs: how do pregnant women solve them, Pharm. World Sci. 16 (1994) 254–259.
9) Oppenheimer JH, Schwartz HL. Molecular basis of thyroid hormone-dependent brain development. Endocr Rev 1997;62–75.
10) LaFranchi SH, Hollowell JG. Is thyroid inadequacy during gestation a risk factor for adverse pregnancy and developmental outcomes? Thyroid 2005;60–71
11) Negro R, Stagnaro-Green A. Clinical aspects of hyperthyroidism, hypothyroidism, and thyroid screening in pregnancy. Endocr Pract 2014;597–607
12) Lazarus J. CGDK DGL, et al. editors. Thyroid regulation and dysfunction in the pregnant patient. EndoText: South Dartmouth, MA; 2016.
13) Thorpe-Beeston JG, Nicolaides KH. Fetal thyroid function. Thyroid 1992;07–17.
14) Contempre B, Calvo R, Campbell S. Detection of thyroid hormones in human embryonic cavities during the first trimester of pregnancy. J Clin Endocrinol Metab 1993;19–22.
15) Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. N Engl J Med 1994;(16):1072–8.
16) Stagnaro-Green A, Alexander E, Azizi F, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011;81–125
17) Alexander EK, Brown RS, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 2017;15–89.
18) Saini A, Panchani R, Gupta N, Tripathi S. Two cases of fetal goiter. Indian J Endocrinol Metab 2012;58–60.
19) Kurtoglu S, Ozdemir A. Fetal neonatal hyperthyroidism: diagnostic and therapeutic approachment. Turk Pediatri Ars 2017;1–9.
20) Ranzini AC, Kung M, Limbachia A, Ultrasonography of the fetal thyroid: nomograms based on biparietal diameter and gestational age. J Ultrasound Med 2001;3–7.

21) Brenta G, Vaisman M, Bravo PP, et al. Clinical practice guidelines for the management of hypothyroidism. Arq Bras Endocrinol Metabol 2013.

22) Stagnaro-Green A, Abalovich M, Mestman J, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during prenancy and postpartum. Thyroid 2011;1081e125.

23) Yazbeck CF, Sullivan SD. Thyroid disorders during pregnancy. Med Clin N Am 2012;235e56

24) Davis LE, Leveno KJ, Cunningham FG. Hypothyroidism complicating pregnancy. Obstet Gynecol 1988;72:108–12

25) Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526–34

26) Singer PA, Cooper DS, Levy EG, et al: Treatment guidelines for patients with hyperthyroidism and hypothyroidism.

27) Stagnaro-Green A, Abalovich M, Mestman J, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during prenancy and postpartum. Thyroid 2011;21:1081e125.

28) Ban Y, Concepcion E, Tomer Y. Linkage analysis of thyroid antibody production: evidence for shared susceptibility to clinical autoinmune thyroid disease. J Clin Endocrinol Metab 2008;93: 3589e96

29) Cooper, D. S. & Laurberg, P. Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol. 1, 238–249 (2013).

30) Casey, B. M. et al. Subclinical hyperthyroidism and pregnancy outcomes. Obstet. Gynecol. 107, 337–341 (2006).

31) Tan JYL, Loh KC, Yeo GSH, Chee YC. Transient hyperthyroidism of hyperemesis gravidarum. BJOG 2002;683–8.

32) Klein I, Becker DV, Levey GS: Treatment of hyperthyroid disease. Ann Intern Med 1994.

33) Burrow GN: Thyroid function and hyperfunction during gestation. Endocr Rev 14:194-202, 1993

34) Davis LE, Lucas MJ, Hankins GDV, et al: Thyrotoxicosis complicating pregnancy. Am J Obstet Gynecol 160:63-70, 1989

35) The management of thyrotoxicosis in pregnancy. N Engl J Med 313:562- 565, 1985

36) Neonatal goiter after maternal propylthiouracil therapy. J Clin Endocr 25:403411, 1965

37) Klatskin EH, Gene1 M: Intellectual development in children whose mothers received propylthiouracil during pregnancy. Yale J Biol Med 51:151-156,1978

38) The management of thyrotoxicosis in pregnancy. N Engl J Med 313:562- 565, 1985

39) Rubin PC: Beta-blockers in pregnancy. N Engl J Med 305:1323-1326, 1981

40) Amino N, Barbour LA, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2007; 92 (suppl): S1–47

41) Marqusee E, Lawrence J, Fischer GA, .Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med 2004;241–49.

42) Alcaraz G, Kleiman-Rubinsztein J, et al. The relationship of preconception thyrotropin levels to requirements for increasing the levothyroxine dose during pregnancy in women with primary hypothyroidism. Thyroid 2010; 20: 1175–78

43) Stagnaro-Green A, Alexander E, et al, and the American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011; 21: 1081–125.

44) De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012; 97: 2543–65.

45) Becker DV, Braverman LE, Delange F,et al. Iodine supplementation for pregnancy and lactation-United States and Canada: recommendations of the American Thyroid Association. Thyroid. 2006;16:949-51

46) Glinoer D, Lemone M, Bourdoux P, De Nayer P, et al. Partial reversibility during late postpartum of thyroid abnormalities associated with pregnancy. J Clin Endocrinol Metab. 1992;74:453-7.

47) Glinoer D. Management of hypo- and hyperthyroidism during pregnancy. Growth Horm IGF Res. 2003;13 Suppl A:S45-54.

48) Haddow JE, McClain MR, Lambert-Messerlian G, et al, and the First and Second Trimester Evaluation of Risk for Fetal Aneuploidy Research Consortium. Variability in thyroid-stimulating hormone suppression by human chorionic [corrected] gonadotropin during early pregnancy. J Clin Endocrinol Metab 2008; 93: 3341–47.

49) Glinoer D, De Nayer P, Meuris S. Serum levels of intact human chorionic gonadotropin (hCG) and its free alpha and beta subunits, in relation to maternal thyroid stimulation during normal pregnancy. J Endocrinol Invest. 1993;16:881-8.

50) Alexander EK, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 2017;27(3):315–89.

51) Roti E, Minelli R, Salvi M: Management of hyperthyroidism and hypothyroidism in the pregnant women. J Clin Endocrinol Metab 81:1679-1682, 1996

52) Nguyen CT, Sasso EB, Barton L, Mestman JH. Graves' hyperthyroidism in pregnancy: a clinical review. Clin Diabetes Endocrinol 2018;4:4.

53) Patil-Sisodia K, Mestman J. Graves hyperthyroidism and pregnancy: a clinical update. Endocr Pract 2010;16(1):118–29.

54) Lazarus J. CGDK DGL, et al. editors. Thyroid regulation and dysfunction in the pregnant patient. EndoText: South Dartmouth, MA; 2016.

55) Adali E, Kolusari A, Kurdoglu M .The use of plasmapheresis for rapid hormonal control in severe hyperthyroidism caused by a partial molar pregnancy. Arch Gynecol Obstet 2009;279(4):569–71.

56) Vyas AA, Vyas P, Fillipon NL, Vijayakrishnan R, Trivedi N. Successful treatment of thyroid storm with plasmapheresis in a patient with methimazole-induced agranulocytosis. Endocr Pract 2010;16(4):673–6.

57) K.D.Tripathi, "Essentials of medical pharmacology". 7th edition 2013, drugs of thyroid drug. Page no. 252-256. Good man and Gill mans, "Pharmacological basic of therapeutics" , 13th edition 2017, pharmacotherapy for thyroid drug. Page no. 800-802.