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Pharmacology of Hypothyroidism and Hyperthyroidism in pregnancy

M.D.THESIS

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2019

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ABSTRACT

Hypothyroidism is a disease that results when the thyroid gland does not produce enough hormones. There are several causes of hypothyroidism, which includes: autoimmune thyroiditis, iodine deficiency and so on. Hypothyroidism can occur in pregnancy, and this disease can be either overt or subclinical during gravidity. The symptoms of hypothyroidism include poor concentration, extreme weakness, abnormal skin changes, and swelling of the extremities. It is difficult to assess hypothyroidism in pregnancy because this disease mimics symptoms of pregnancy. Therefore, screening of high-risk patients has proven to be beneficial in recent times. Furthermore, the drug of choice for hypothyroidism remains levothyroidise, and there was a diagrammatic representation in my thesis of how it should be used in treating hypothyroidism. Untreated hypothyroidism in pregnancy can lead to serious, life-threatening complications such as: placenta abruption and so on. Poor fetal neurological development might be a resultant consequence of maternal hypothyroidism.

The thyroid gland is a distinct anatomy comprising of right left, superior and pyramidal lobes. The right and left lobes are connected to each other vis an isthmus. It also has fascias and suspensory ligaments, which forms the bulk of the connective tissues. The principal arteries of the thyroid gland are the superior and inferior thyroid arteries. The venous drainage of the thyroid gland is as follows: the superior and middle thyroid vein drains into the internal jugular vein. While the inferior thyroid veins drain into the right brachiocephalic vein. The functional unit of the thyroid is the follicle, which contain colloid particles that aid in the production of thyroid hormone.

Hyperthyroidism is a condition where there is overproduction of thyroid hormones. There are clinical manifestations of the disease like heat intolerance, weight loss, skin and hair changes as well as mental changes. Early diagnosis and prompt management of thyrotoxicosis and hyperthyroidism were discussed below. Methimazole, propylthiouracil are used to treat hyperthyroidism in pregnancy. Beta-blockers are used as adjunctive therapy and are especially used in controlling thyroid storms. The side effects of these medications during pregnancy should be considered before initiating therapy..

ABBREVIATION

AACE- American Association of Clinical Endocrinology

ATA- American Thyroid Association

ATDS- Anti-thyroid Drugs

CATS- Controlled Antenatal Thyroid Study

ER- Endoplasmic Reticulum

GFR- Glomerular Filteration Rate

HCG- Human Chorionic Gonadotropin

MMI- Methimaazole

PTU- Propylthiouracil

PPH- Post-partum Haemorrhage

RBF- Renal Blood Flow

SCM- Sternocleidomastoideus Muscle

T3- Thyronine Hormone

TBG- Thyroid Binding Globulin

TBII- Thyroid Binding Inhibiting Immunoglobulin

TPO- Thyroperoxidase enzyme

TRH- Thyroid Releasing Hormone

TRab- Thyroid Stimulating Hormone Receptor Antibody

TSH- Thyroid Stimulating Hormone

TSI- Thyroid Stimulating Immunoglobulin

UC- Umblical cord

CHAPTER 1

1.0 INTRODUCTION

Hypothyroidism is an endocrinological condition occurring as a result of the thyroid glands being underactive. In such cases, the above named gland does not synthesize sufficient thyroid hormones. It was first reported by medical practitioners in the 19th century and its treatment was discovered half a century ago. This disorder is known to predispose the patient to a host of other diseases that may subsequently cause more debilitation. The age distribution for hypothyroidism is between 60 and above. There are multifarious causes of hypothyroidism such as: autoimmune diseases, iatrogenic causes, gravidity, hypopituitarism and paucity of iodine. One of the leading causes of hypothyroidism in the developing world however, is insufficient iodine obtained in meals.

Hypothyroidism that occurs during gravidity may cause cretinism. Cretinism is a pathological condition that causes growth and mental retardation due to a lack of thyroid hormone. Pregnant women experience physiological changes and this may affect their thyroid hormone functions. An example is that during the first trimester, as HCG hormones increase, the TSH levels may appear to be reduced. In the first trimester, the developing foetus relies solely on the mother for thyroid hormone production. After first trimester, the developing foetus starts to synthesize his or her thyroid hormones (American Thyroid Association (1993)).

The female hormone estrogen increases the proteins that bind to thyroid hormones in the serum. This causes a rise in total thyroid hormones in the blood. An important point to mention is that the free thyroid hormones, meaning hormones not bound to thyroid binding proteins stay normal during pregnancy. The prevailing cause of hypothyroidism during pregnancy is autoimmune thyroiditis also known as Hashimoto's thyroiditis. Thyroid hypertrophy in pregnancy may occur as a result of iodine deficiency especially in developing countries. Poorly managed hypothyroidism in pregnancy may lead to serious complications if not fatal ones. Complications like maternal anaemia, PPH and so on (American Thyroid Association (1993))

Maternal hypothyroidism may be overt or subclinical. The subclinical hypothyroidism is insidious because if left unchecked and unscreened, it causes serious problems to the development of the fetus.

Furthermore, there is a plethora of FDA endorsed medications used in the treatment of hypothyroidism. Drugs like levothyroxine can be used in treatment of hypothyroidism. Liothyronine which is a synthetic T3 which is used in combination with levothyroxine aids in ameliorating this condition.

1.1 ANATOMY OF THE THYROID GLAND

The thyroid is a brown –coloured, richly vascularized tissue located in the lower portion of the neck, between the fifth cervical and the first thoracic. In adults, it is estimated to have an average weight of 25-30g, which increases in size during gravidity and menses. The thyroid gland is approximately 12-15mm in height, and lays untop of the tracheal rings. The gland can have a semblance of H or U alphabet depending on each individual. The gland has two lobes which are approximately 50-60mm in length. The lobes are attached to the median isthmus. It also has two poles called superior and inferior poles. This gland may be present without the isthmus every now and again. The superior poles branches off laterally at the lamina of the thyroid cartilage. The inferior pole branches off at the level of the fifth portion of the thyroid cartilage. The pyramidal lobe shoots out of the isthmus or the left lobe sometimes. It is connected to the levator of thyroid gland at the level of the hyoid bone. There are two parathyroid glands located posteriorly to the lateral lobes of the thyroid gland (Dorion D (2017)).

The thyroid gland has a visceral fascia which encloses it and this fascia, which comes from the deep cervical fascia. There is an anterior suspensory ligament that connects the superior part of the thyroid gland to the larynx. The posterior suspensory ligament connects the posteriomedial part of the gland to the trachea and cricoid cartilage. More importantly, the attachment of the thyroid gland to the larynx enables the gland move during swallowing. The thyroglossal ducts may leave remnants that become cysts of the thyroid tissue. Verily the recurrent laryngeal nerve passes through the posterior suspensory or Berry's ligament. This is usually located between the isthmus and the tongue's foramen caecum. Additionally, the sternothyroid muscles are located lateral to the thyroid gland. The sternohyoid and the superior belly of the omohyoid muscles are located anteriorly. The SCM covers these previously mentioned muscles inferiorly. The avascular facia convalesces the sternohyoid and sternothyroid muscles at the midline (Dorion D (2017)).

The illustration below depicts the anatomy of the thyroid gland with their lobes, and their blood supply.

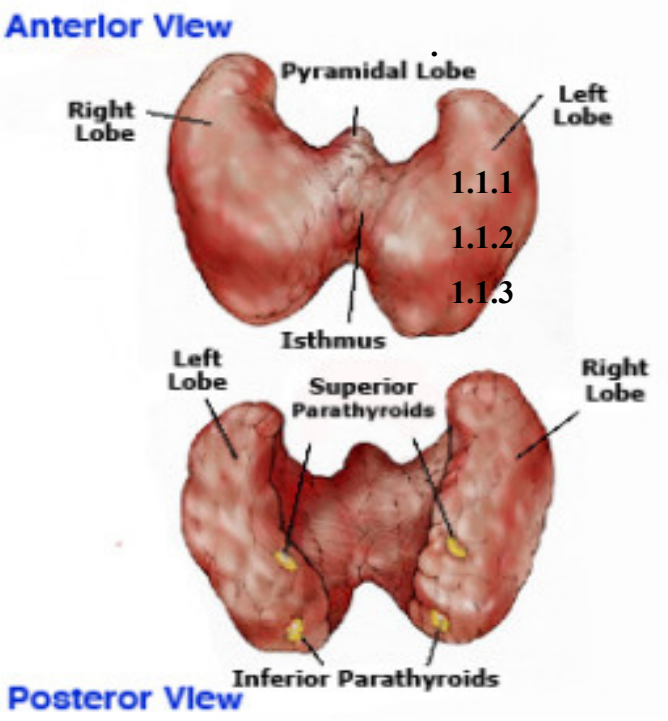

Figure 1 Anatomy of the Thyroid Gland (thyroidsurgerymd.com (2018)).

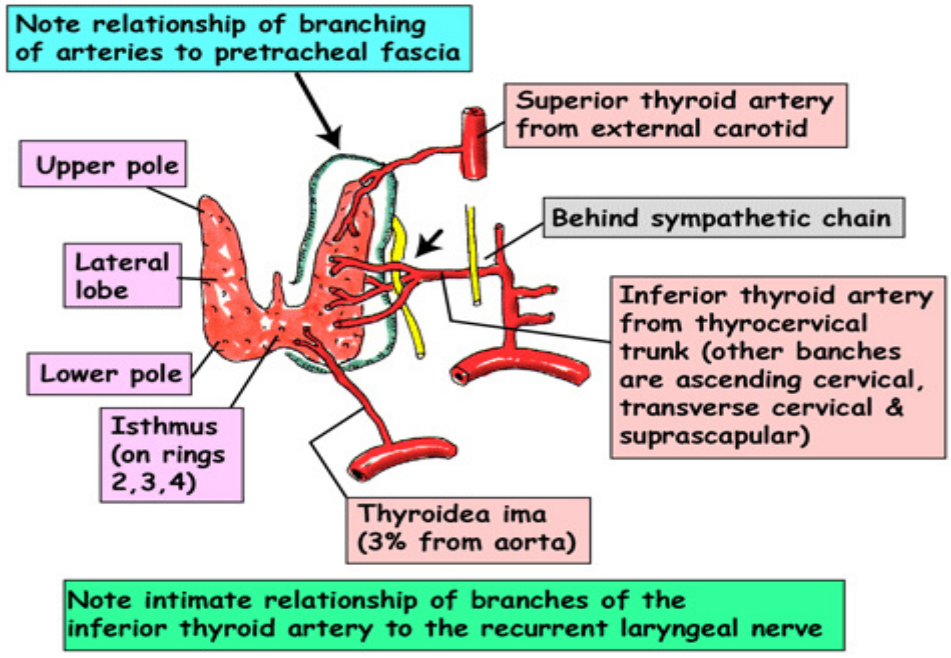

Figure 2 Blood Supply of the Thyroid gland (khalidalomari.weebly.com (2018))

1.2 HISTOLOGY OF THYROID

There is a capsule that attaches to it and this structure divides the gland into further lobes and lobules. Follicles are found inside the lobule. The follicles are lined with simple cuboidal epithelium and have a cavity, which is filled with colloid. The colloid contains glycoproteins that are rich in iodine and thyroglobulin. These colloids are encircled with vessels nerves and so on. The epithelial cells are composed of two cells called follicular or principal cells and parafollicular cells. As already mentioned above, the follicular cells contain colloid, which produces thyroid hormone precursors. Parafollicular cells on the other hand are responsible for the production of calcitonin. Calcitonin hormone regulates circulating calcium levels (Dorion D (2017)).

The figure herein reveals the follicular cells of the thyroid gland which are filled with colloid.

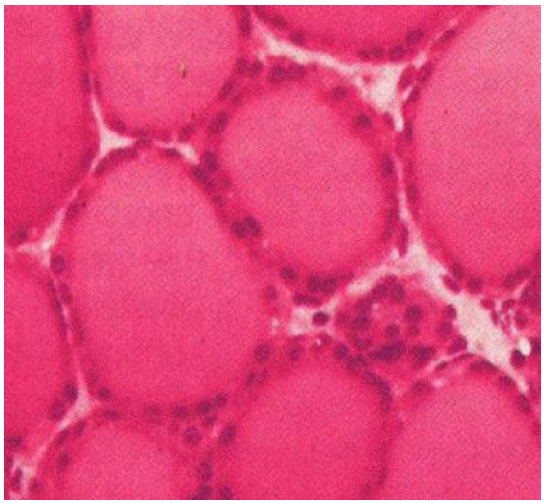

Figure 3 Follicular cells (Dorion D (2017)).

1.3 BLOOD SUPPLY OF THE THYROID GLAND

The superior, inferiorior thyroid arteries are the major vascular arteries of the thyroid gland. The superior thyroid artery comes from the external carotid artery and in rare occasions, the common carotid artery. They run below the omohyoid and sternohyoid muscles and along the surface of the lateral lobe anteriorly. At the isthmus, they anastomose with the artery on the opposite side. And, run together with the superior laryngeal nerve (Dorion D (2017)).

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The inferior thyroid arteries originate from the thyrocervical trunk, travel upward and enter the tracheoesophageal groove; they then turn around the carotid sheath medially. The inferior thyroid artery has a changeable relationship with the recurrent laryngeal nerve. It enters the tracheoesophageal groove and exits at the thoracic outlet. The thyroidea ima supplies the thyroid gland with blood, and particularly the isthmus, from time to time. This vessel arises from the aorta or the innominate arteries (Dorion D (2017)).

There are three veins that drain the thyroid gland. The superior thyroid vein drains into the internal jugular vein while the middle thyroid vein moves laterally to drain into the internal jugular vein as well. The right inferior thyroid vein moves in front of the innominate artery and empties into the right brachiocephalic vein. However, the inferior thyroid vein on the sinister side of the body drains into the left brachiocephalic vein. From time to time, the inferior thyroid veins join to form a thyroidea ima vein and this forms a tributary to the left brachiocephalic vein (Dorion D (2017)).

The schematic diagram below provides adequate illustration.

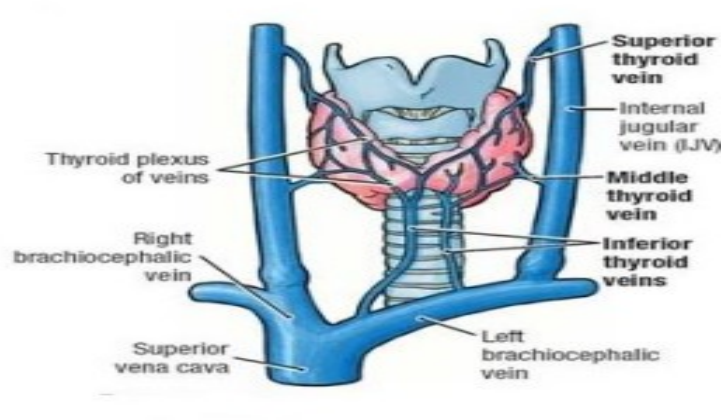

Figure 4 Veins of the Thyroid Gland (www.lifeinsuranceblog.com (2013))

The Lymphatic drainage of the thyroid gland is composite. Foremost, the lymph flows into the periglandular nodes then to the prelaryngeal nodes, pretracheal nodes and finally into the paratracheal lymph nodes. These veins course along the recurrent laryngeal nerve and enter into the mediastinal lymphnodes, which eventually drain into the internal jugular vein. Hence, in thyroid cancer, there may be metastases to internal jugular vein because; the tumor invades the pre and para-tracheal nodes. This will eventually lead to lymphatic obstruction (Dorion D (2017)).

CHAPTER 2

2.1 PHYSIOLOGY OF THE THYROID GLAND

The thyroid gland synthesizes thyroid hormones, which are T3 and T4. These hormones are responsible for the regulation of metabolism such as respiration, cellular growth and maturation. The gland has a capsule which contains follicles and as previously mentioned in chapter 1, the follicles are the functional units of this gland. Thyroperoxidase is produced in the thyroid gland; the ER of thyrocytes produces the above-named enzyme. TPO oxidizes iodine, which forms the bulk of T3 and T4 hormones. T4 is converted to T3, which is the active hormone in body tissues (Wier and Farley (2006)).

There is negative feedback between the hypothalamo-pituitary-thyroid axis in order for hormones to be released into the bloodstream. Therefore, a decrease in T3/T4 hormone causes an automatic response in hypothalamus to release TRH, which stimulates the pituitary gland to dissipate TSH. These responses eventually lead to the increase of T3 hormones or less frequently, T4 hormones. Conversely, when there is an increase in T3 hormones, an inverse reaction occurs, which lead to the reduction of TRH and TSH respectively (Wier and Farley (2006)).

There are diverse opinions concerning the normal range of serum TSH. The AACE places the value of serum TSH between 0.3-3.0mIU/L while the National Clinical Biochemistry's value is between 0.4-2.4mIU/ L. There has been a generally accepted value that the upper limit does exceed 4.12mIU/ L. Thyroxine binding globulin binds to serum T3 and T4 even though free T3 and T4 are present in tissues. Furthermore, research has shown that high iodine concentration in the blood reduces the T3 and T4 levels.

2.1.1 THYROID FUNCTION IN PREGNANCY

Pregnancy usually induces normal changes in thyroid function. Foremost, there is more excretion of iodide from the serum. This occurs as a result of the increase in GFR and the RBF. Normally, an average individual needs 150micrograms/day of iodine in the diet. However, recommended intake of iodine increases to 200micrograms/day during pregnancy and lactation. There is a similarity in structure between TSH's beta-subunit and that of HCG; though, HCG has a poor stimulating effect on thyroid hormones. Towards the beginning of

the second trimester, a sizeable amount of pregnant women demonstrate an increase in unbound T4 and a decrease in TSH (Wier and Farley (2006)).

The table below aptly illustrates the thyroid functions in pregnancy

Table 1: Physiological Alterations of Thyroid Functions in Pregnancy (slideshare.com (2014))

Maternal Status	*TSH Initial Screening*	*Free T4*	*Free Thyroxine index (FTI)*	*Total T4*	Total T3	*Resin Triiodothyronine uptake (RT3U)*
Hyperthyroidism	*Decrease*	*Increase*	*Increase*	*Increase*	*Increase or no change*	*Increase*
Pregnancy	*No change*	*No change*	*No change*	*Increase*	*Increase*	*Decrease*
Hypothyroidism	*Increase*	*Decrease*	*Decrease*	*Decrease*	*Decrease or no change*	*Decrease*

From the table above, we can clearly deduce that there is no change in TSH and free T4 hormones. But a change is clearly seen in Total T3 and Total T4respectively.

Moreso, resin triiodothyronine decreases during the period of gravidity. Furthermore, it is of clinical benefit to mention that during gravidity, there is an increase in vascularisation and a slight hypertrophy of thyroid gland. As described above, there is a similarity in structural homology between beta-HCG and the TSH. Hence, during the first trimester, there will be a slight alteration of the thyroid functions. The HCG causes a decline in the TSH hormones, present in the blood (Cignini et al. (2012)).

The TBG levels in the serum also increase as a result of an increase in estrogen hormones. Additionally, the serum TBG increases due to augmented synthesis in the liver. The estrogen increases and causes an increase in the half-life of the TBG. The half-life of TBG extends from 15 minutes to 3 days . Secondly, Total T3 and T4 in the serum increase during the early stages of gravidity. These hormones reach a steady state during the second trimester, and their concentrations are 30-100% more than before pregnancy (Cignini et al. (2012)).

It is therefore important to note that some sources insist that there is a decrease in the concentrations of free or unbound T4 and T3. Other sources, as previously mentioned, state that the concentrations of free T4 and T3 increase or remain the same. Nometheless, it has been established that at term, pregnant women have a depressed concentration of free or unbound T3 and T4 (Cignini et al. (2012)).

Thyroglobulin concentrations are often augmented. This eschews that the thyroid gland's activity is increased. Maternal thyroid hormones provide the fetus with essential iodine and required hormones. The thyroid hormones of the mother are essential for the proper development of the fetal brain structure. After 12 weeks, the fetal thyroid hormones starts concentrating, and the production of thyroid hormones commences (Cignini et al. (2012)).

The graph below shows the concentrations of thyroid hormones in relation to gravidity.

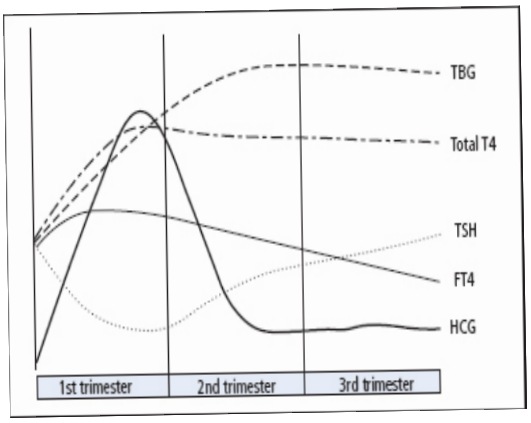

Figure5 Thyroid Hormone Levels in Various Trimesters (Basicmedicalkey.com(2016*))*

2.1.2 PHYSIOLOGY OF FETAL THYROID

The thyroid gland of fetus begins its formation at the midline of the anterior pharyngeal floor-and then moves posteriorly to the final position-at the seventh gestational week. By week 12 of gestation, the fetal thyroid can catch iodine and can also produce thyroxine on the fourteenth gestational week. TSH, T4, and TBG increase steadily by gestational week thirty-six. Before the increase occurs, the hormones do not rise exponentially however, until gestational week eighteen to twenty. Furthermore, T3 hormones do not demonstrate increased concentrations that are equal to those observable in the adult population. This is solely due to the fact that placenta type 3 deiodinase converts T4 to reverse T3 (Sahay RH and Nagesh VS (2012)).

There is no mammoth translocation of TSH across the placenta. However there is a marked transportation of T3 and T4 across the placenta. This may be possible explanation as to the development of congenital hypothyroidism; due to the fact that T4 in the UC of new born babies can be 50% of the normal. There is also a transfer of anti-thyroid drugs, iodine, TSI, and TRH (Sahay RH and Nagesh VS (2012)).

Table 2: Transport of Thyroid Hormones and Antibodies Across The Placenta. (Sahay RH and Nagesh VS (2012)).

Substance	**Transfer across placenta**
Iodine	Transport across placenta, both by diffusion and active transport
Thyroxine	There is a certain level of transport that is observable. It is mostly seen in the first trimester
TSH	Transportation of this substance across the placenta is poor
TRH	Heavily transported across the placenta
Antibodies	Anti-TPO, Anti-TG, TBII and TSI, can cross placenta freely and TSI can cause transient neonatal hypothyroidism and TBII can cause transient neonatal hypothyroidism.

The figure below has been inserted to this sub-heading for further illustration.

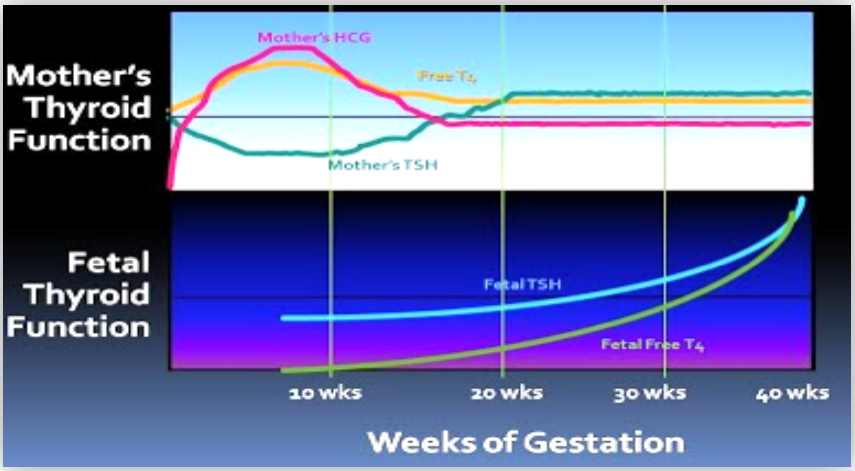

Figure 6 Maternal and Fetal Thyroid Changes in Pregnancy (www.houstonendocrine.com (2018))

2.2 EPIDEMIOLOGY & ETIOLOGY OF HYPOTHYROIDISM IN PREGNANCY

The prevalence of hypothyroidism during gravidity is around 0.3-0.5%. It is however appraised to be 2-3% for subclinical hypothyroidism. There are plethora causes of hypothyroidism during pregnancy. These include the following: radiation ablation post hyperthyroidoism or thyroid cancer treatment, thyroidectomy, ectopic thyroid, lymphocytic hypophysitis, certain medications-rifampycin and phenytoin- and so on. However, the most prevalent cause of hypothyroidism is autoimmune thyroiditis. But iodine deficiency also poses as one of the main causes of hypothyroidism all around the world (Sahay RH and Nagesh VS (2012)).

2.2.1 AUTOIMMUNE THYROID DISEASE

Many studies have indicated that there is a risk of miscarriage in pregnant women with this disease. But studies of mortality have not been entrenched, and the presence of antibodies could probably be an indication of autoimmune recurrent miscarriages. There has also been a rise in perinatal mortality and macrosomia babies in studies that were conducted on women with autoimmune thyroid disease (Sahay RH and Nagesh VS (2012)).

TPO antibodies have been found in euthyroid women on IVF therapy. These TPO antibodies have been reported to be responsible for miscarriages in these women. There was a study carried out by Negro et al. that demonstrated a correlation between euthyroid women with thyroid antibody positivity and preterm delivery and the probability of having a baby with

respiratory distress. Furthermore, treatment with LT4 in euthyroid gravidity patients with autoimmune disease evoked a decrease in bad obstetric results. Mannisto et al. carried out another study- and discovered that thyroid problems and antibodies during pregnancy may lead to an eventual development of thyroid disease later on. Clinical hypothyroidism may be a precursor to the development of diabetes (Sahay RH and Nagesh VS (2012)).

2.2.2 SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism is marked by an augmented level of TSH, but a normal level of free T3 and free T4. Its prevalence during gravidity is 2-5% -and they do not have clinical symptoms. There is a likelihood of women with this condition to have TPO positive antibodies than women without a thyroid disease. Moreso, the etiology of this type of disease is similar to that of hypothyroidism with clinical manifestation (Sahay RH and Nagesh VS (2012)).

There are several studies that point out that subclinical hypothyroidism causes bad obstetric results. There are extant recommendations that thyroxine replacement should be used in women with subclinical hypothyroidism. Notwithstanding, though thyroxine replacement has been demonstrated to improve maternal and fetal outcomes, there has been no sufficient evidence to show that this treatment improves fetal neurological development (Sahay RH and Nagesh VS (2012)).

2.2.3 ISOLATED MATERNAL HYPOTHYROXINEMIA

Isolated maternal hypothyroxinemia is diagnosed when the levels of free T4 are low and the TSH levels are normal. The prevalence of this condition is between 1-2%. There was a FASTER study carried out among hypothyroxinemic women with normal TSH levels. There was an augmented odds ratio for preterm labour (1.62, 95% CI 1.00–2.62), macrosomia (1.97, 95% CI 1.37–2.83), and gestational diabetes (1.70, 95% CI 1.02–2.84). The results were not usually steady. Next, Casey et al. conducted a study, which revealed that this condition in the first part of gravidity did not cause any bad obstetric outcome (Sahay RH and Nagesh VS (2012)).

There were many studies that revealed that infants and preschoolers of mothers with decreased free T4 in the serum- at 12-20 weeks of gestation- demonstrated a reduced intelligence. They also demonstrated lower behavioural and psychological ranges as opposed to children born to euthyroid women. Furthermore, there is no extant study that has revealed

positive results of administering levothyroxine medication to hypothyroxinemic gravid women (Sahay RH and Nagesh VS (2012)).

The figure below shows certain types of hypothyroidism and concentrations of T4

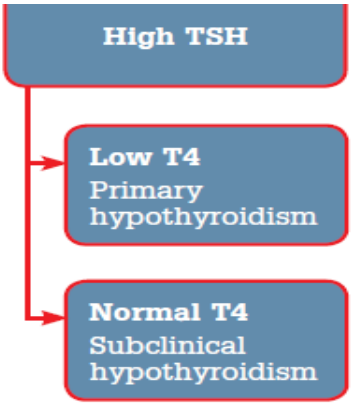

Figure 7 Types of Hypothyroidism And T4 Levels (www.dietvsdisease.org (2017))

2.3 DIAGNOSIS OF HYPOTHYROIDISM

The gold standard of diagnosis for this disease is the thyroid function test. As already stated in the previous pages, primary hypothyroidism is marked by increased serum TSH levels. The elevation of serum free T4 levels portends subclinical hypothyroidism and hypothyroidism with clinical manifestations. The alteration in TBG levels causes an augmentation in total hormone levels. TSH levels according to trimester changes are avant garde and have an upper limit of 2.5µiu/ml in the first trimester; also, the upper limit in the second and third trimester is 3µiu/ml. The reason is due to stimulatory effects of hCG. Measuring TPO and TG antibodies remains the confirmatory tests for autoimmune hypothyroidism (Sahay RH and Nagesh VS (2012)).

The figure below represents a flow chart of diagnosis of hypothyroidism.

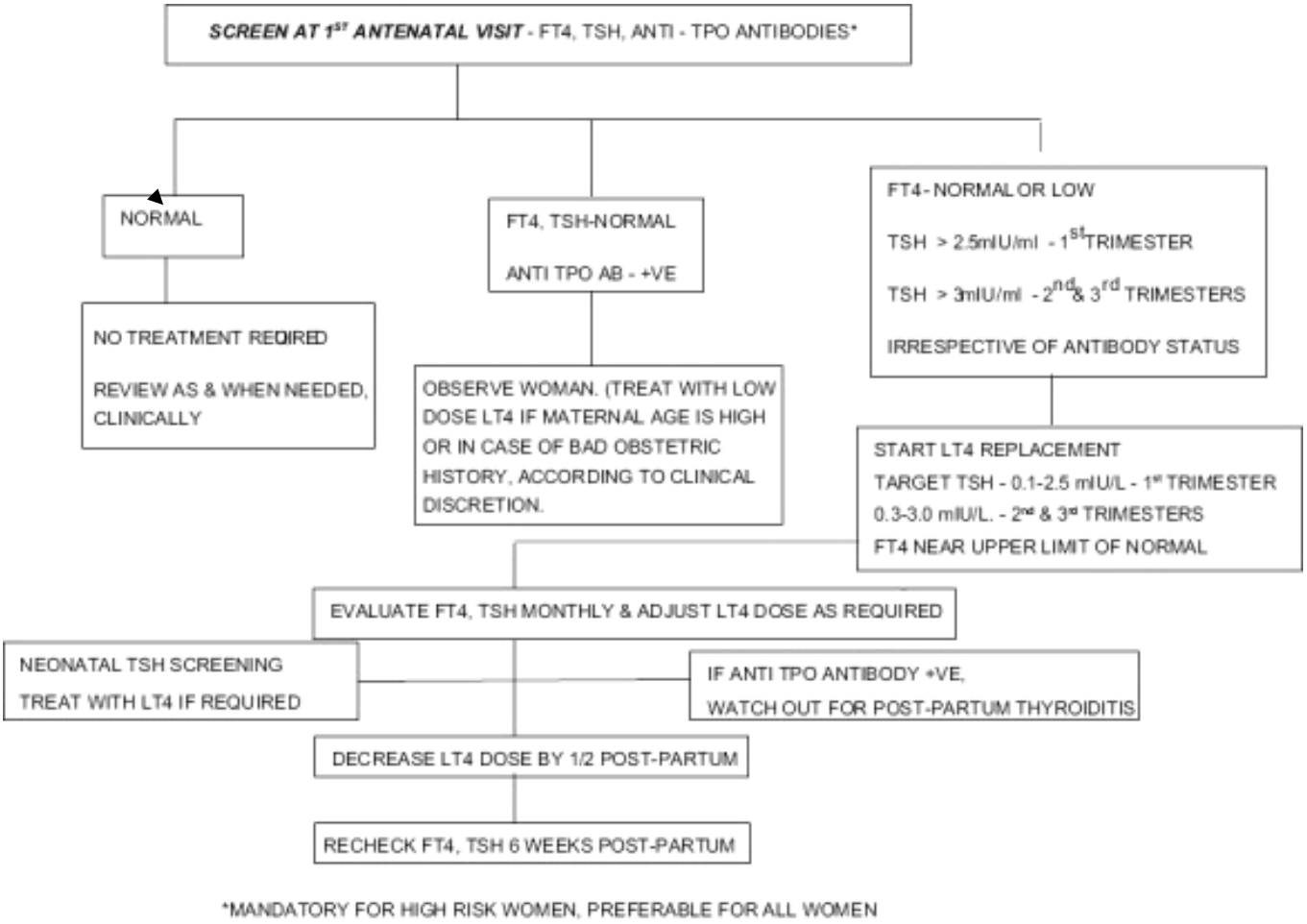

Figure 8 Diagnosis of Hypothyrodism *(*Sahay RH and Nagesh VS (2012)).

2.3.1 UNIVERSAL SCREENING vs. TARGETED CASE FINDING FOR HYPOTHYROIDISM

Targeted case finding has been a go-to method of choice over screening in the past, because of feasibility, affordability and a dearth of studies that reveal the advantage of screening over the above-mentioned finding. Screened patients have a history of type 1 DM, a pre-extant thyroid disease, hereditary factors, previous surgery on the head and neck, and so on. Thyroid, Endocrine and Obstetrics organization has heralded a position of not recommending a universal screening. But universal screening has come to the forefront in recent times, due to awareness of retardation of cognitive development, caused by maternal hypothyroidism (Sahay RH and Nagesh VS (2012)).

Vaidya et al. carried out a study and revealed that if clinicians screened only women with high chances of developing hypothyroidism, there will be 30% under reported cases of women with subclinical or overt hypothyroidism. The study concluded that universal screening is better than screening only targeted cases. Negro et al examined the results of bad obstetrics outcomes, after treatment using universal screening vs. targeted case finding, in patients with thyroid problems. Unfortunately, universal screening did not prove superior to targeted case finding in reducing bad obstetric outcomes. There was no evidence of obvious bias as the study however, separated women into two groups. All the women in the universal groups were screened: 482 women in high risk group and 1798 low-risk factor-women (Sahay RH and Nagesh VS (2012)).

Moreso, women in the targeted case finding group were grouped thus: 454 high-risk category women and 1828 low-risk category women. Levothyroxine was administered to women presumed to have hypothyroidism. Invariably, women each high-risk group of universal screening and targeted case findings received therapeutic measures. However, only low-risk women in the universal screening group received treatment; while the same favours were not extended to women in the targeted case finding group. Negro et al. pointed out the results of both arms in line with the aim of the study. (Sahay RH and Nagesh VS (2012)).

Currently, Lazarus et al. is conducting a trial known as CATS, which aims at finding out whether universal screening and levothyroxine treatment reduces adverse maternal outcomes. This clinical trial would run concurrently for eight years. This study collects serum samples of pregnant women prior to gestational week 16. The participants free T4 and TSH are measured adequately (Sahay RH and Nagesh VS (2012)).

Levothyroxine is scheduled to be administered to women whose free T4 levels are under the 2.5 percentile, and whose serum levels TSH are above the 95th percentile. If the results of the above-mentioned trial are made known, there would be a clearer picture as to the superiority of one screening method over the other. As fore stated universal screening seems to be the avant garde method of screening-over targeted case findings according to reports- in recent times (Sahay RH and Nagesh VS (2012)).

2.4 CLINICAL MANIFESTATIONS

There are a variety of symptoms during gravidity that are look like patients with hypothyroidism that are non-pregnant. These symptoms include the following:

- Constipation (Ross DS (2018))
- Cold intolerance (Ross DS (2018))
- Weight gain (Ross DS (2018))
- Tiredness

The symptoms can mask those of pregnancy hence, many patients remain asymptomatic. The figure below illustrates the clinical manifestation of hypothyroidism in details.

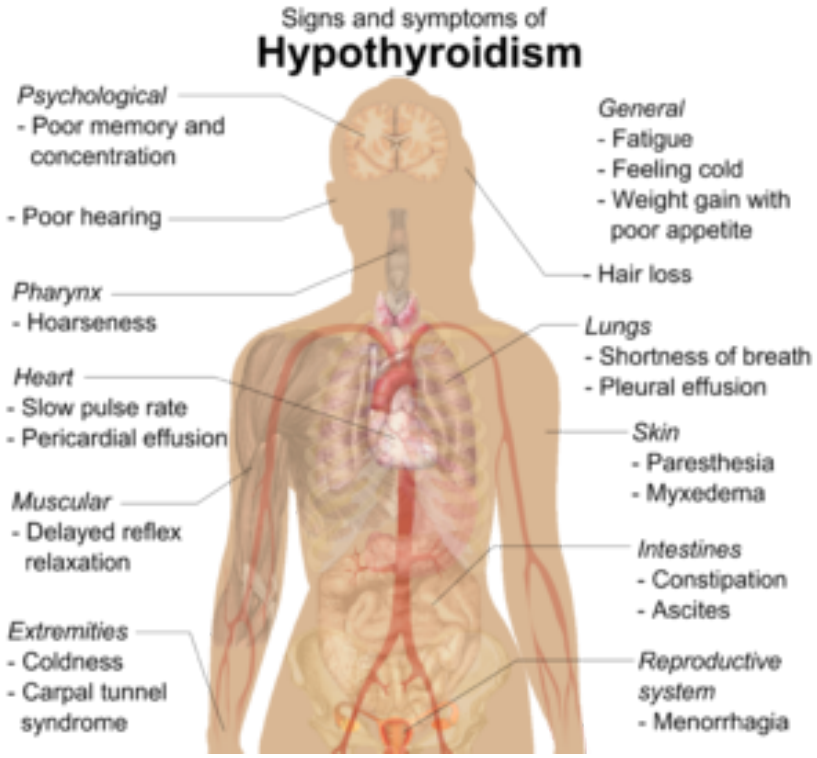

Figure 9 Symptoms of Hypothyroidism (www.wikepedia.org (2014))

2.5 LEVOTHYROXINE DRUGS FOR HYPOTHYROIDISM

This medication can be used to preclude neonatal low birth weight and so on.

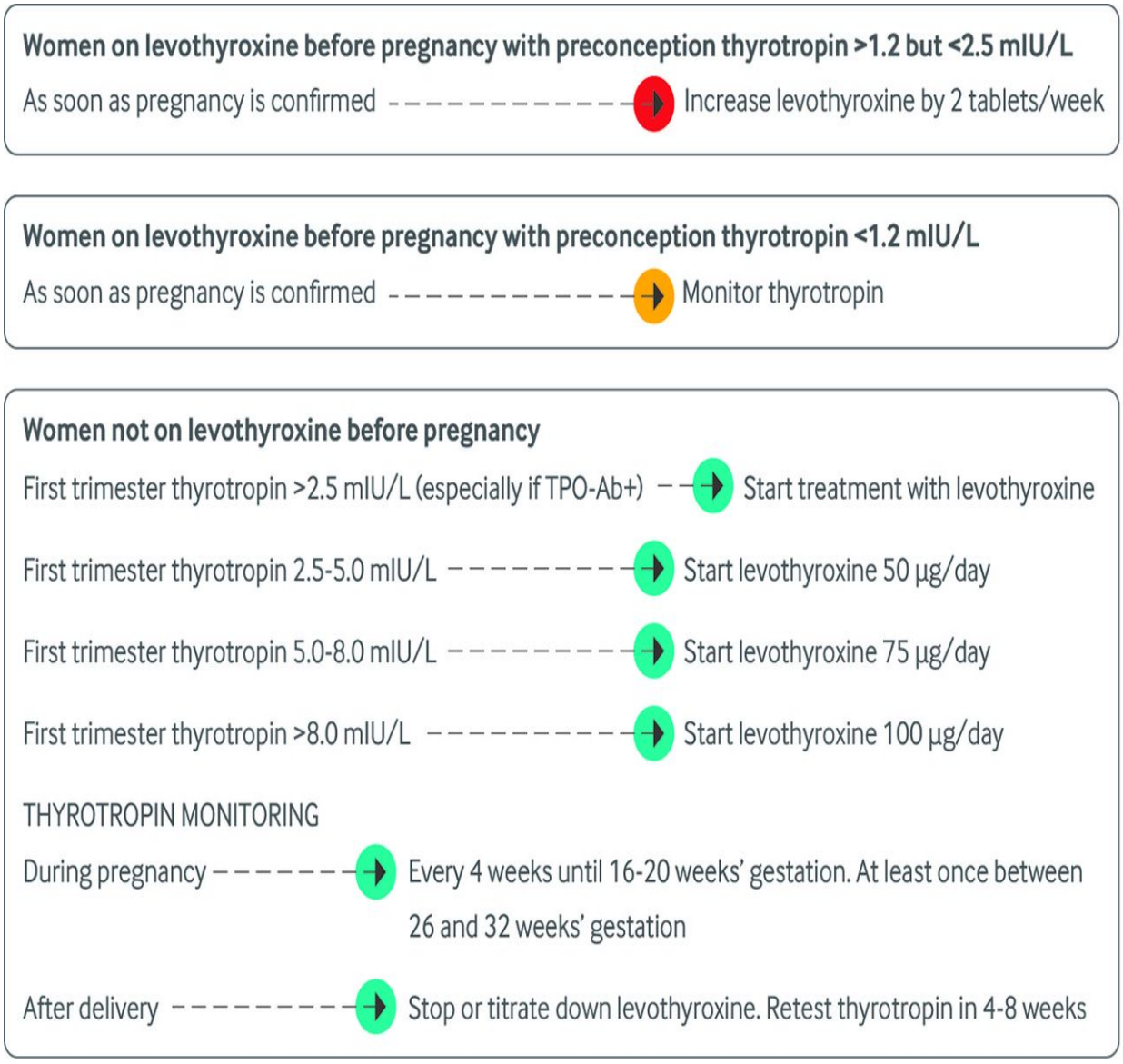

Figure 10 Treatment of Subclinical Hypothyroidism (www.bmj.com(2014))

As the diagram above portrays, women who were initially on levothyroxine before pregnancy should augment their dose to two tablets of levothyroxine per day immediately after the diagnosis of pregnancy.In certain studies there has been a certain prevalence ofpregnant women with subclinical hypothyroidism is 3 to 15%. Subclinical hypothyroidism has many adverse effects for mother like gestational diabetes, preeclampsia and pregnancy induced hypertension. Only two studies have highlighted how levothyroxine is used in pregnant women with subclinical hyperthyroidism (www.bmj.com(2014)).

CHAPTER 3

HYPERTHYROIDISM IN PREGNANCY

Hyperthyroidism can be properly defined as the increase in thyroid hormones synthesis. On the other hand, thyrotoxicosis is a clinical consequence of the overproduction of thyroid hormones in the circulation regardless of origin. There is an inordinate increase in iodine uptake in this condition. Thyrotoxicosis that is not in conjunction with hyperthyroidism can be caused by other sources of thyroid hormone production that is not within the thyroid gland. This condition may demonstrate a low uptake of radioactive iodine by the thyroid gland. There are two common types of hyperthyroidism. These include: overt hyperthyroidism and subclinical hyperthyroidism (Leo et al. (2016)).

Overt hyperthyroidism is clinically demonstrated by low TSH and raised T4 and T3; whereas, subclinical hyperthyroidism low TSH but the thyroxine and tri-iodothyronine levels are normal (Leo et al. (2016)).

3.1 EPIDEMIOLOGY AND ETIOLOGY OF HYPERTHYROIDISM

The prevalence of this condition is 1.3% in the United States and 0.8% in Europe respectively. Furthermore, the prevalence of overt hyperthyroidism is 0.5% in the USA and 0.5-0.8% in Europe albeit. This disease is more frequent in older women than it is in men. There is limited data for races with the likelihood of developing hyperthyroidism. There are some data, however, that indicate Caucasoid races having a higher chance of developing this condition than other races. In iodine deficient regions, the incidence of developing hyperthyroidism is slightly higher. There has been a demonstrable decrease in incidence of hyperthyroidism after initiating programs that aim at bringing awareness to utilizing iodinated salt in diet of individuals. In Sweden, in the 2000s, the incidence of grave's disease was between 15-30 cases out of 100 000 people (Leo et al. (2016)).

As for the aetiology of hyperthyroidism, the most common cause in iodine-rich areas remains Graves's disease. There are many causes of Graves's disease that are both of genetic and environmental origin. The causes may have been as a result of autoimmunity, which comes from the development of auto-antibodies that stimulate the follicular cells, that is the TSH receptor antibodies. The genetics of Graves's disease have been demonstrated in many studies. But in those data, low penetrance has been eschewed because the concordance rates were low on the data reports (Leo et al. (2016)).

The Graves's disease genes include CD40, CTLA4, PTPN22, and FCRL3. The thyroid auto-antigens are thyroglobulin and so on. The other causes of Graves' disease include smoking, female population, stress, vitamin D deficiency, deficiency of selenium, immunomodulators, destruction of the thyroid gland, Yersinia enterocolitica, and a few others. Yeresinia enterocolitica may be a likely cause of this ailment due to the mimicry of TSH receptors. The disease is high in female population due to the distorted X inactivation, chromosomal factors and others. Thyrotropin thyrotoxicosis is not a common cause of hyperthyroidism (Leo et al. (2016)).

More aetiology factors of thyroid deficiency include: solitary toxic adenoma, toxic multinodular goiter, which occur in regions with iodine deficiency. The previously mentioned aetiologies are common amongst the geriatric population. In such cases, thyroid nodules start synthesizing thyroid hormones away from TSH receptor antibodies or TSH-initiated commands. Trophoblastic tumours cause TSH to simultaneously over-stimulate TSH receptors and HCG (Leo et al. (2016)).

The figure below properly portrays the causes of hyperthyroidism in an illustrative manner.

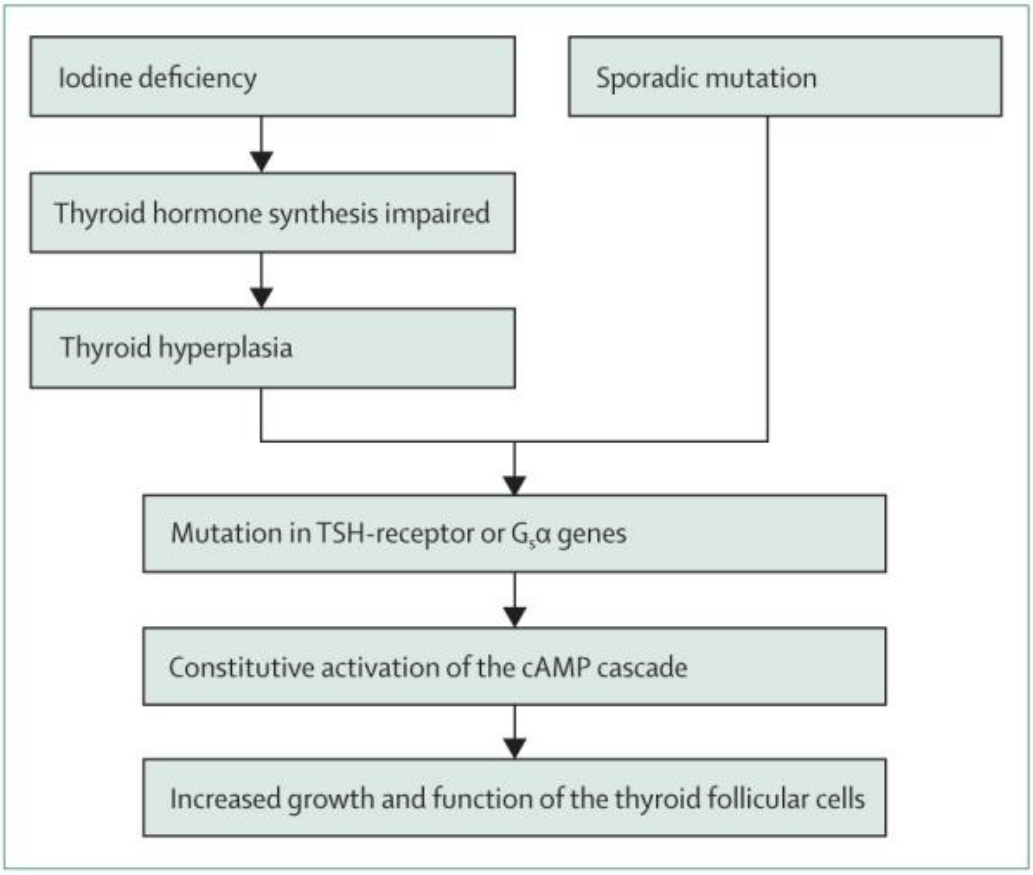

Figure 11 Pathomechanism of Thyroid Autonomy (Leo et al. (2016)).

3.2 THRYOTOXICOSIS WITHOUT HYPERTHYROIDISM

The causes of this condition are somewhat fleeting and uncommon. People with non-overt thyroiditis, thyroiditis acquired after birth, subacute painful thyroiditis can experience damage of thyroid cells, which causes a spontaneous dissipation of thyroid hormones. Drug induced thyrotoxicosis can be caused by the following: amiodarone, lithium and interferon - alpha. There are iatrogenic causes of thyrotoxicosis which occur after consuming large amounts of thyroid hormones. This type of thyrotoxicosis can be demonstrated by the low thyroglobulin concentration in the serum. The rarest cause, however, remains ectopic hyperthyroidism- caused by the metastases of thyroid cancer and struma ovarii (Leo et al. (2016)).

3.3 CLINICAL SYMPTOMS OF HYPERTHYROIDISM AND THYROTOXICOSIS

There are many effects caused by the over-production of thyroid hormones; these effects may affect many parts of the body such as: the brain, heart, excretory gland of the skin and so on. Symptoms such as diaphoresis, heat intolerance, perturbing sleep, intolerance to heat, generalized weakness, cachexia and excessive thirst. On physical examination, demonstrable symptoms include: tarchycardia and so on (Leo et al. (2016)).

The table below delineates the clinical symptoms of hyperthyroidism

Table 3: Clinical Symptoms of Thyrotoxicosis (Leo et al. (2016)).

Constitutional	Anxiety, sleep disturbance, inability to concentrate properly Physical findings: hyperreflexia, muscle weakness
Pulmonary symptoms	Difficulty in breathing and shortness of breath Physical findings: fast breathing
Cardiovascular	Palpitations Physical Findings: fast heart rate, atrial fibrillation and so on.
Gastrointestinal	Nausea, Emesis, diarrhoea Physical examination: tenderness of abdomen

Table 3: Clinical Symptoms of Thyrotoxicosis (Leo et al. (2016)).

Cutaneous symptoms	Diaphoresis Physical Examination: skin is warm and moist
Ocular symptoms are specific for Graves' disease	Double vision, eye swelling, pain located behind the eyes and so on. Physical Examination: Proptosis, chemosis, ophtalmoplegia, periorbital edema and so on
Reproductive symptoms	Disturbance of the menstrual cycle

There are other symptoms of grave disease such as thyroid acropachy, thyroid dermopathy, ophtalmopathy and a few others. However, ophtalmopathy is a noticeable feature in a quarter of patients with Grave's disease. The symptoms of these include: swelling around the orbital area, proptosis, and double vision. In nodular goitre, symptoms like difficulty in swallowing, orthopnea, oesophageal or tracheal compression can be observed. While, pain in the anterior neck is seen in subacute thyroiditis (Leo et al. (2016))..

Thyroid dermopathy is a delphic manifestation of Graves ' disease and most of the patients with this particular symptom, have ophtalmopathy. This condition is characterised by pigmentation in the skin and keratosis around the pretibial region of the body. The acropachy is the most recherché symptom of this condition and it is characterised by the clubbing of the digits of the hands and toes (Leo et al. (2016)).

3.4 DIAGNOSIS OF HYPERTHYROIDISM

TSH in serum has the greatest specificity and sensitivity. Measure free T4, and serum free T4, and free /total T3 should be measured as well. These measurements are done so that there is a clear delineation between subclinical and overt hyperthyroidism. It is useful for determining conditions that causes augmented thyroid hormone concentrations and disorders that provoke a normal or only partially increased TSH. For instance, patients with TSH-secreting pituitary tumors and peripheral resistance to thyroid hormones are conditions that provoke the previously mentioned concentrations. The techniques used to determine the etiology of thyrotoxicosis broadly differ. These differences are due to the array of various people, ethnicities, social strata and so on (Leo et al. (2016)).

ATA and AACE suggest that radioactive iodine uptake test should be done if there is a suspicion for hyperthyroidism and thyrotoxicosis. These can be excluded if there has already been an established clinical diagnosis of Graves' disease. Utilization of TSH receptor antibodies are opted for in certain countries of Asia and Europe. However, in the USA there are certain guidelines that opt for the use of the previously mentioned receptors for diagnosing Graves' disease. These antibodies are to be used when the use of radioactive iodine as a means of diagnosis is contraindicated and not readily available (Leo et al. (2016)).

There would be diffused uptake after the consumption of radioactive iodine in a patient with Graves' disease. In a patient with multinodular goiter, radioiodine uptake would be normal or high but demonstrate an irregular and asymmetrical pattern. There is a local pattern of radioactive iodine uptake observed in patients with toxic adenoma. However, patients with thyrotoxicosis have a low radioactive iodine uptake.

The figure below adequately summarizes the diagnosis of both subclinical, overt hyperthyroidism and thyrotoxicosis.

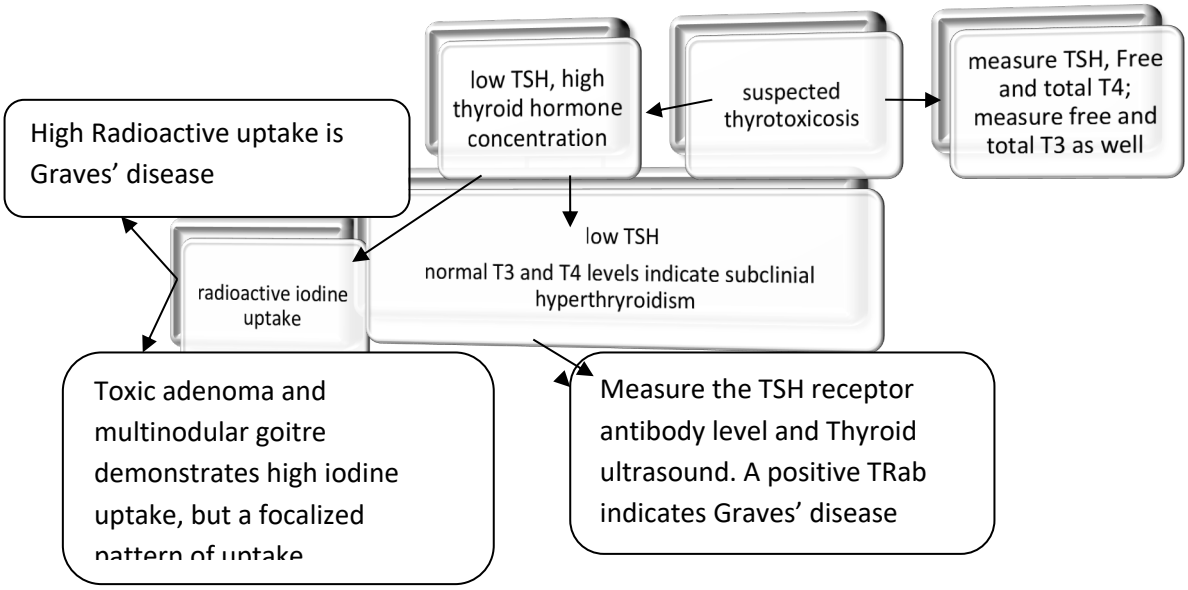

Figure 12: Guidelines for Diagnosing Hyperthyroidism (Leo et al. (2016)).

CHAPTER 4

4.1 TREATMENT OF HYPERTHYROIDISM IN PREGNANCY

Immediate treatment of hyperthyroidism is essential to preclude problems with the overall health of the mother and baby. Though the use of anti-thyroid drugs in the treatment of this condition has not proven to yield beneficial effects in the amelioration adverse pregnancy outcomes; the use of anti-thyroid drugs is appropriate for the treatment of other types of hyperthyroidism in pregnancy. Transient biochemical hyperthyroidism is a condition that necessitates medical attention. It is caused by the rise in hCG levels during the primeval stages of pregnancy. (Anderson S and Laurberg P (2016)).

ATD inhibit the production of thyroid hormones in the thyroid gland. The notable ATDS include methimazole, propylthiouracil, and carbimazole. These drugs tend to cross the placenta, and may cause fetal hypothyroidism. There is a serious consternation among researchers about potential adverse health effects on the fetus - as a result of consumption of the above medication. To further buttress my point, in 1972 there was an initial report of the correlation of birth defects with the consumption of ATDs. The use of radioactive iodine in treatment of hyperthyroidism during gravidity is strongly contraindicated. Thyroidectomy is performed during the second trimester when other methods of treating hyperthyroidism fail. . (Anderson S and Laurberg P (2016)).

Propylthiouracil is the main drug used to treat hyperthyroidism in gravidity. This drug is mostly used as a drug of choice in America. This is owing to the fact that methimazole causes congenital defects like aplasia cutis, choanal atresia, abnormal facies and a retardation in development. However, a recent cohort study that was carried out--proving that the net risks of developing a congenital defect as a result of the consumption of methimazole, was not greater than the risks when consuming other drugs that are not teratogenic. Likewise, three other studies did not demonstrate any augmentation in congenital defects as a result of exposure to methimazole (Inoue et al. (2009))

The predilection for propylthiouracil over methimazole is due to the fact that this medication does finitely cross the placental surface. This is of course in comparison to methimazole. In Europe and many developing continents, methimazole is used as a treatment of hyperthyroidism in pregmancy (Inoue et al. (2009)).

There was a scare that propylthiouracil had a tendency of propuylthiouracil causing liver toxicity and this caused consternation among pregnant users of propylthiouracil. That prompted the American thyroid association to recommend propylthiouracil for pregnant women with hyperthyroidism. Furthermore, the authors assessed a Danish cohort study comprising of 564 children exposed to PTU, 159 children exposed to MMI and PTU, and 1097 infants exposed to MMI. The authors revealed that there was an increased rate of congenital defects when exposed to the above mentioned drugs early in pregnancy. The fetus exposed to PTU had a birth defect of 8.0%; 9.1% birth defect for MMI exposure and a whopping 10.1% birth defect while exposed to MMI and PTU (Rivkees SA (2013)).

PTU in the previously assessed study was mostly linked to causing abnormalities in the face and neck, pulmonary valve and artery stenosis and so on. MMI was associated with chroanal and esophageal atresia, omphalocoele, omphalomesenteric duct anomalies and the list goes on. The combination of PTU and MMI was known to cause some abnormalities in the urinary tract. Furthermore, Yohishira et al. revealed the denouements of 6744 pregnant, Japanese women with Graves' disease. 1426 people out of these women were administered MMI as treatment for their disease condition. While 1578 women were given PTU in order to manage the disease. However, 2065 women were not administered any medication for their ailment. The results showed that the prevalence of birth defects were as follows: 4.9% for MMI group, 2.1% for the untreated category and finally, 1.9% for the PTU group (Rivkees SA (2013)).

According to Yoshihara et al. the adverse effects of PTU included syndactyly, imperforate anus, hydronephrosis, intestinal malrotation and so on. Moreso, at the Eunice Kennedy Shriver Institute of Child Health and Human Development, the International Clearing House of Birth Defects used a case controlled study to further assess the issue. The results were revealed that 127 children born to women on anti-thyroid medication demonstrated the following; 52 situs inversus, obstruction of the cardiac outflow and renal dysgenesis were all associated with PTU. While the same adverse effects of MMI could as delineated earlier, could also be observed in this study (Rivkees SA (2013)).

The FDA carried out a study that the authors also decided to investigate. There were 375 side effects associated with PTU administration and 625 adverse effects of MMI. A total of 19 reports were published associating PTU to causing birth defects. And an additional 40 reports showed that MMI caused birth defects (Rivkees SA (2013)).

4.2 BETA ADRENERGIC ANTAGONISTS

These medications were initially used a djunctive therapy to antithyroids because they were unable to completely eradicate symptoms. Propanolol and nadolol have a characteristic of inhibiting T4 to T3. Most of these patients however have temporary relief while on propanolol four times daily. Notwithstanding, drug compliance can be ameliorated by using nodolol or atenolol once a day. Beta-blockers are used to treat thyrotoxicosis caused by trauma infections and so on. Propanolol is beneficial before a thyroidectomy and is good to be continued for 7 to 10 days. This drugs help to curb sympathetic actions in the cells. Levothyroxine can be used as an adjunct to aid patient's recovery during euthyroid (Lee LK and David (2009))

There are however certain contraindications to the use of beta blockers. Such contraindications include obstructive pulmonary disease, cardiac compromise, insulin dependent diabetes and so on. The use of these medications can cause neonatal hypoglycaemia, bradycardia, growth restriction and so on. But the benefits of using these classes of drugs are greater than the risks and it should be used (Bernstein PS (2003)).

4.3 OTHER ASPECTS OF TREATMENT OF HYPERTHYROIDISM

Iodine is not recommended in pregnancy due to the fact that it could potentially lead to neonatal goiter and hypothyroidism. Iodides can easily diffuse through the fetal placental tissue and their thyroids are sensitive to the inhibition by iodides. Iodides should only be used for a short period of time and before a surgery is carried out. Furthermore, surgery is not advisable during gravidity. It would however be required if the hyperthyroidism is refactory to medications for hyperthyroidism (Bernstein PS (2003)).

Radioactive iodine is an absolute contraindication during gravidity. Studies show that treatment with 2,2 rad for hyperthyroidism and there was a risk for congenital hypothyroidism when it was given after gestational weeks 10 or 12. But if the radioactive iodine was given after gestational week 12, it is then advisable to give PTU for 10days to suppress fetal exposure. First trimester exposure can cause chromosomal and congenital abnormalities. It may also lead to the development of certain blood cancers. Women treated with radioactive iodines are encouraged to use a method of contraception inorder to advoid getting pregnant, for roughly about half a year (Bernstein PS (2003)).

CONCLUSION

Hyperthyroidism and hypothyroidism remains one of the leading endocrinological diseases in the world today. The consequences and total disease burden of hypothyroidism is worrisome. As already stated before, hypothyroidism and hyperthyroidism in pregnancy, can pose a serious threat to the mother and developing fetus. Therefore, early diagnosis and screening of high risks groups will prevent untoward consequences. One of the drugs that have been approved for the treatment of hyperthyroidism in gravidity is propylthiouracil. It is however adviseable to use propylthiouracil only in the first trimester because of hepatotoxicity. Thereafter, switching to methimazole in the second and third trimester has been proven to be beneficial.

Levothyroxine should be used to treat hypothyroidism in pregnancy, but there should be primacy in monitoring the excretion mechanism and dosage of levothyroxine. This is particularly important in pregnant patients with arrhythmias and other types of cardiac anomalies because, this medication is known to worsen it.

In many clinical trials, especially those that have been actively carried out by Li J et al, LT4 supplements have proven to be advantageous in improving symptoms and overall results for pregnant women with thyroid anomalies.

Researchers continue to look for new ways to treat maternal hypothyroidism and hyperthyroidism. The aim of new therapies should be to minimize side effects of ant-thyroid medications as well as ameliorate patient's symptoms.

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