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Assessment of Thyroid Function in Pregnant Women From Rimal Health Center, Gaza City

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نتيجة الحكم على أطروحة ماجستير

بناءً على موافقة عمادة الدراسات العليا بالجامعة الإسلامية بغزة على تشكيل لجنة الحكم على أطروحة الباحثة/ رغدة عبد اللطيف عبد اللطيف راضي لنيل درجة الماجستير في كلية العلوم/ قسم العلوم الحياتية/تحاليل طبية وموضوعها:

Assessment of thyroid Function in pregnant Women From Rimal health center, Gaza Strip

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Assessment of Thyroid Function in Pregnant Women From Rimal Health Center ,Gaza City.

Abstract

Background. Pregnancy is associated with significant but reversible changes in thyroid function tests results, which are as a result of a normal physiologic state. Pregnancy influences thyroid function and may bring to light mild and latent disorders. This study focused on thyroid hormones as the human fetal thyroid does not secrete thyroid hormones until approximately 12 weeks of gestation, the fetus is dependent until that time on a supply from the maternal circulation. Thyroid dysfunction has been related to obstetrical complications such as premature delivery, gestational hypertension, preeclampsia, and placental abruption.

Objective: to assess the maternal thyroid function in the first trimester of pregnant women from Rimal health center-Gaza city.

Materials and methods. A cross sectional study was designed with 90 normal pregnant women who were randomly selected from the first trimesters attending *Rimal Health Center* and 80 randomly selected non-pregnant healthy female controls. Age range in both groups was 18-40 years. Thyroid function tests were carried out by measuring serum levels of thyroid stimulating hormone (TSH), free thyroxin (FT4), and free triiodothyronine (FT3). They were measured using Microparticles Enzyme Immunoassay (MEIA). SPSS was used to analyse obtained data.

Results: The results showed that there was a significant increased between the non pregnant women group and pregnant women for FT4 and FT3 where the p-value is 0.04 and 0.030 respectively. the mean TSH levels of pregnant women was lower than the mean level of non pregnant but did not show significant difference in first trimester compared with non-pregnant women. Also there was a significant statistical difference between the groups of different age for FT4 and FT3 where the p- value was 0.034 and 0.038 among the non pregnant women group. On the other hand, there was no statistically significant relationship between thyroid function in pregnancy and family history of thyroid problems, genetic disease, and hypertension among women in the study sample.

Keywords. Pregnancy, thyroid function, TSH, FT4, FT3, Gaza, Palestine.

مستخلص

تقيم وظائف الغدة الدرقية لدى النساء الحوامل من مركز الرمال الصحي في مدينة غزه

تتعرض المرأة في أثناء فتره الحمل لعدد من التغيرات الفسيولوجية بما في ذلك ما يحدث في الغدة الدرقيـــة وهدفت هذه الدراسة التركيز على هرمونات الغدة الدرقية لما لها من الأهمية كما أن النمــو الطبيعـي لمــخ الجنين يخضع لإمداد منتظم لهرمونات الغدة الدرقية، ولأن القليل منها أو الكثير يمكن أن يعوق النمو العصبي للجنين، ولكن الخلل في الغدة الدرقية يؤدي إلى حدوث مضاعفات الولادة مثل: الولادة المبكــرة ، ارتفــاع ضغط الحمل ، تسمم الحمل ، انفكاك المشيمة. وقد أجريت الدراسة لمعرفه التغيرات في اختبــارات وظـائف الغدة الدرقية خلال الشهور الثلاثة الأولى لدى النساء الحوامل.

الهــدف : تقييم وظائف الغدة الدرقية لدى النساء الحوامل في الشهور الثلاثة الأولى من الحمل في مدينه غزة.

الطرق : تم دراسة عينه مكونه من *170* سيدة، ومقسمه إلى مجموعتين:المجموعة الأولى مكونه من *90* سيده حامل في الفترة الأولى من الحمل والمجموعة الثانية مكونه من(*80*) سيدة غير حامل، وقد تم فحص كل من هرمون**TSH,FT4 and FT3** .

النتائج : أظهرت الدراسة وجود علاقة ذات دلاله "إحصائية "ما بين الحمل،ووظائف الغدة الدرقية لكــل مــن هرموني الثيروكسين، وهرمون ثلاثي ثايرونين بين السيدات الحوامل والسيدات غير الحوامل، وكان هنــاك فرق ما بين الهرمون المحفز للغده الدرقية أيضا ولكن لم يكن ذا دلاله إحصائية، كما أظهرت النتائج وجــود علاقة ذات دلاله إحصائية بين عمر السيدة ووظائف الغدة الدرقية لدى السيدات غير الحوامل، كذلك أظهرت النتائج إلى عدم وجود علاقة ذات دلاله إحصائية بين كل من (ضغط، الدم ،تــاريخ المــرض فـي العائلــة ،الأمراض الوراثية) مع وظائف الغدة الدرقية على مستوى حجم عينه البحث.

الكلمات المفتاحية/ الحمل، الثيروكسين، ثلاثي ثايرونين،الهرمون المحفز للغده الدرقية،غزه،فلسطين.

Dedication

To Allah's most sacred religion 'Islam'', which
urged us to seek knowledge on its first
revelation

To my father and mother who have supported
me all the way since the beginning of my
study.

To my sister Nahla

To my brother's, Hussam Eslam, Mohammad
To all my family

To all my friends

To all of them I dedicate this work

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It is impossible to convey, in a couple of sentences, my gratitude to many people for helping me to learn and who cooperation made this work possible. All praises and glory are due to **Allah** for all the bounty and support granted to me.

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I wish to present my thanks to the people who served as healthy controls in my study.

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List of abbreviations

AITD   Autoimmune Thyroid Disease
DIT   di-iodinated tyrosine
hCG   Human Chorionic Gonadotropin,
LH   Luteinizing Hormone
MEIA   Microparticles Enzyme Immunoassay
MCT8   Monocarboxylate Transporter 8
MIT   mono-iodinated tyrosine
OATP1C1   Organic Anion Transporter
PTH   Parathyroid Hormone
SRIH   Somatostatin
TG   Thyroglobulin
TBG   Thyroid Binding Globulin
TH   Thyroid Hormones
TSH   Thyroid-Stimulating Hormone
TPO   Thyroperoxidase
TRH   Thyrotropin-Releasing Hormone
T4   Thyroxine
T3   Triiodothyronine

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INTRODUCTION

CHAPTER (1)
INTRODUCTION

1.1 Overview

Pregnancy is associated with significant but reversible changes in thyroid function which are a result of normal physiologic state and hormonal changes that alter thyroid function (1). These changes mean that laboratory tests of thyroid function must be interpreted with caution during pregnancy (2).

Thyroid function change during pregnancy due to the influence of two main hormones (a) human chorionic gonadotropin (hCG), the hormone that is measured in the pregnancy test. Human chorionic gonadotropin can weakly turn on the thyroid and the high circulating hCG levels in the first trimester may result in a slightly low thyroid stimulating hormone (TSH) in the first trimester and then return to normal throughout the duration of pregnancy (1). TSH suppression is a transient phenomenon and TSH concentrations generally remain within non pregnant reference intervals in normal pregnancy (3). (b) estrogen, the main female hormone, estrogen stimulates thyroid binding globulin (TBG) formation and increases its half life, with maximal TBG levels around 20 weeks, leading to increases in serum thyroxine levels (4). Estrogen increases the amount of thyroid hormone binding proteins in the serum which increases the total thyroid hormone levels in the blood since >99% of the thyroid hormones in the blood are bound to these proteins (5).

However, measurements of "Free" hormone (that is not bound to protein, representing the active form of the hormone) usually remain normal (6). The thyroid is functioning normally if the TSH, free thyroxine (T4) and free triiodothyronine (T3) are all normal throughout pregnancy. Therefore, thyroid function is frequently assessed during pregnancy, both to evaluate suspected thyroid abnormalities, and to monitor the status of pre-existing thyroid disease (7). As thyroid disorders are the most common endocrinology disorders of childbearing age (8). Moreover, thyroid disorders may affect both the pregnant woman and the developing fetus; where thyroid hormones having important role in embryogenesis and fetal development (9). The fetus is completely dependent on the mother for thyroid hormone (10).

Thyroid disorders such as chronic thyroiditis, hypothyroidism, Graves' disease, etc. are relatively common in pregnant women (11). Disorders of the thyroid include both overt and mild/subclinical hypothyroidism and hyperthyroidism and goitre. Hypothyroidism is estimated to occur in 0.3-0.5% of pregnancies (12) Subclinical hypothyroidism appears to occur in 2-3% (13) .Hyperthyroidism during gestation, usually caused by Graves disease, is rare (0.2%). (14)

Uncontrolled hyperthyroidism and hypothyroidism are associated with serious maternal, fetal, and neonatal morbidity, and mortality. Maternal complications include miscarriage, pregnancy-induced hypertension, preterm labor, placental abruption, heart failure, and thyroid storm. Fetal and neonatal complications include stillbirth, low birth weight, goiter, hyperthyroidism, and hypothyroidism (15,16,17).

1.2 Problem statement

Checking routinely (screening) for possible thyroid problems was not considered important in pregnant women, where pregnant women with thyroid disease do not always develop symptoms, and when they do, these symptoms can sometimes be attributed to the pregnancy itself. It is only considered important when pregnant women had the typical symptoms of hypothyroidism or hyperthyroidism. Lack of early diagnosis increase the risk of pre-term birth, placental abruption, fetal death, and impaired neurological development in the child. For these reasons, it is important to ensure optimal maternal thyroid function during pregnancy so accurate laboratory assessment of maternal thyroid function is important. Moreover, for Gaza city thyroid function in pregnant women have not been carried before.

1.3 Objectives

The general objective of this study is to assess the maternal thyroid function in the first trimester among pregnant women from Rimal Health Center, Gaza city.

The specific objectives of the study are:

1- To determine thyroid hormone levels in the first trimester of pregnancy.

2- To observe any changes in thyroid hormone levels.

3- To study possible relation between family history of thyroid problem, genetic disease, hypertension and age.

1.4 Significance

This research will be conducted for the first time in Gaza city. According to preliminary statistics obtained from a group of obstetric & gynecology physicians (ob|Gyn), many pregnant women suffer thyroid dysfunction. The assessment of thyroid function in pregnant women will draw the attention of (ob|Gyn) physicians to deal properly with this problem including screening of thyroid hormones during pregnancy.

LITERATURE REVIEW

CHAPTER (2)
LITERATURE REVIEW

2.1 The critical role of the thyroid gland

The thyroid gland plays a vital role in the overall body function during all stages of life. Although relatively small, it produces hormones that regulate the body's overall metabolism, the rate at which the body produces energy from nutrients. Thyroid hormones influence growth and development, oxygen consumption and heat production, nerve function, and metabolism of lipids, carbohydrates, proteins, nucleic acids, vitamins, and inorganic ions. They also have important effects on other hormone actions (18).

If left untreated, thyroid disease can lead to an increased risk of heart disease, osteoporosis and infertility. An estimated 13 million Americans have a thyroid problem, but more than half remain undiagnosed. Thyroid hormones are particularly important during pregnancy and play a key role in fetal development. Until the fetal thyroid gland is developed at approximately 12 week's of gestation, the maternal thyroid is solely responsible for delivering thyroid hormone, which is essential to fetal brain development. The placenta and amniotic fluid transfer small but crucial amounts of thyroid hormone from the mother to the fetus.(19)

2.2 Thyroid gland

2.2.1 Anatomy of the thyroid gland

`The thyroid gland is one of the largest endocrine glands in the body, weighing 2-3 grams in neonates and 18-60 grams in adults, and is increased in pregnancy. This gland is found in the neck inferior to the thyroid cartilage (also known as the Adam's apple in men) as shown in Figure (2.1). It is a butterfly-shaped organ and composed of two cone- like lobes: right lobe and left lobe, connected with the isthmus. The organ is situated on the anterior side of the neck, lying against and around the larynx and trachea, reaching posteriorly the oesophagus and carotid sheath (20).
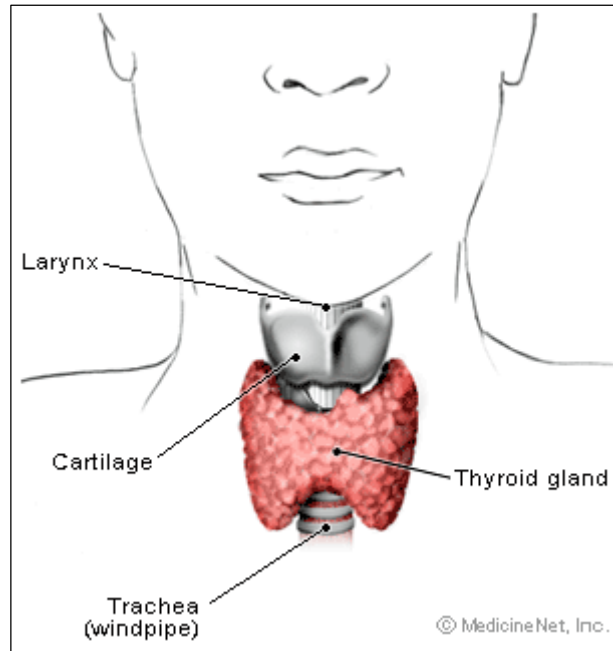
Figure 2.1: Thyroid gland (21)

2.2.2 Physiology of thyroid gland

Thyroid gland produces the hormones T4, T3, and calcitonin . Up to 80% of the T4 is converted to T3 by peripheral organs such as the liver, kidney and spleen. T3 is about ten times more active than T4 (22).

2.3 The thyroid hormones

The thyroid gland secretes two hormones, L-T4 and L - T3. The thyroid hormones are the only iodine-containing compounds with established physiologic significance in vertebrates (23)**.** T4 is the predominant form of thyroid hormone. It's called T4 because it contains four iodine atoms for each hormone molecule. When one specific iodine atom is removed from the T4 molecule, it becomes RT3 or T3, the form necessary for doing the thyroid's job for the body's cells. Nearly all cells have special enzymes inside of them (deiodinases) that remove an iodine from T4 to make it into T3. The thyroid gland usually releases around 80 percent of its hormones as T4 and 20 percent as T3 (24). When this T4 and T3 enter the blood, most of these hormones stick to blood proteins made by the liver, called *thyroid hormone transport proteins.* Thyroid hormones (TH) are transported in serum non covalently bound to three proteins: T4- (TBG), albumin, and transthyretin previously called pre- albumin (25).

The relative distribution of TH among the binding proteins is directly related to both their affinities and concentrations. In steady state conditions, the bound hormone fraction is in equilibrium with a free unbound fraction, which represents a minute amount of the total circulating TH: 0.03% for T4 and 0.3% for T3 (26). The production of thyroid hormones is based on the organization of thyroid epithelial cells in functional units, the thyroid follicles, a single layer of polarized forms envelope of a spherical structure with an internal compartment, the follicle lumen. Thyroid hormone synthesis is dependent on the cell polarity that conditions the targeting of specific membrane protein, either on the external side of the follicle (facing the blood capillaries) or on the internal side and on the tightness of the follicle lumen that allows the gathering of substrates and the storage of products of the reactions. Thyroid hormone secretion relies on the existence of stores of pre-synthesized hormones in the follicle lumen and cell polarity-dependent transport and handling processes leading to the delivery of hormones into the blood stream(23). After concentrating iodide, the thyroid rapidly oxidizes it and binds it to tyrosyl residues in thyroglobulin (TG) followed by coupling of iodotyrosines to form T4 and T3. The process requires the presence of iodide, a peroxidase (TPO), a supply of H_2O_2, and an iodine acceptor protein (TG) (27).

2.3.1 Thyroxine

3,5,3',5'-tetraiodothyronine (T4), a form of thyroid hormones, is the major hormone secreted by the follicular cells of the thyroid gland. Thyroxine is synthesized via the iodination and covalent bonding of the phenyl portions of tyrosine residues found in an initial peptide, TG which is secreted into thyroid granules. These iodinated diphenyl compounds are cleaved from their peptide backbone upon being stimulated by thyroid stimulating hormone. T4 is transported in blood, with globulin (TBG), 99.95% of the secreted T4 being protein bound principally to thyroxine-binding globulin, to transthyretin and serum albumin. T4 is involved in controlling the rate of metabolic processes in the body and influencing physical development. Thyroxine is a prohormone and a reservoir for the active thyroid hormone T3 which is about four times more potent. T4 is converted in the tissues by deiodinases to T3. The "D" isomer is called "Dextrothyroxine and is used as a lipid modifying agent. The half-life of thyroxine once released into the blood circulatory system is about one week (28).

2.3.2 Triiodothyronine

TSH activates the production of T4 and T3. This process is under regulation. In the thyroid, T4 is converted to T3. TSH is inhibited mainly by T3. The thyroid gland releases greater amounts of T4 than T3, so plasma concentrations of T4 are 40-fold higher than those of T3. Most of the circulating T3 is formed peripherally by deiodination of T4 (85%), a process that involves the removal of iodine from carbon 5 on the outer ring of T4. Thus, T4 acts as prohormone for T3. In addition, T3 exhibits greater activity and is produced in smaller quantity. It is the most powerful thyroid hormone, and affects almost every process in the body, including body temperature, growth, and heart rate. The biological half-life is 2.5 days (28).

2.3.3 Calcitonin

An additional hormone produced by the thyroid gland contributes to the regulation of blood calcium levels. Parafollicular cells produce calcitonin in response to hypercalcemia. Calcitonin stimulates movement of calcium into bone, in opposition to the effects of parathyroid hormone (PTH). However, calcitonin seems far less essential than PTH, as calcium metabolism remains clinically normal after removal of the thyroid, but not the parathyroids (29).

2.4 Synthesis of thyroid hormones

The first step in the formation of thyroid hormones (TH) involves the active accumulation of iodide from the extracellular fluid across the basolateral membrane and into the thyroid follicular cell. The protein responsible for this was previously described as the iodide trap or iodide pump. Because the transport into the follicular cell of iodide against its concentration gradient is coupled with transport of sodium, the protein was named the sodium/iodide symporter (NIS) (30). The iodide pump is linked to a Na+-K+-pump, which requires energy in the form of oxidative phosphorylation (ATP) and is inhibited by ouabain. The thyroid absorption of iodide is also inhibited by negative ions (such as perchlorate, pertechnetate, thiocyanate and nitrate), because they compete with the iodide at the trap. In the follicular cell, iodide passes down its electrochemical gradient through the apical membrane and into the follicular colloid. Iodide is instantly oxidised – with hydrogen peroxide as oxidant -

by a thyroid peroxidase to atomic or molecular iodine at the colloid surface of the apical membrane. Thiouracil and sulfonamides block this peroxidase. The rough endoplasmic reticulum synthesises a large storage molecule called thyroglobulin. This compound is build up by a long peptide chain with tyrosine units and a carbohydrate unit completed by the Golgi apparatus. Iodide-free thyroglobulin is transported in vesicles to the apical membrane, where they fuse with the membrane and finally release thyroglobulin at the apical membrane.

At the apical membrane the oxidised iodide is attached to the tyrosine units (L-tyrosine) in thyroglobulin at one or two positions, forming the hormone precursors mono-iodotyrosine (MIT), and di-iodotyrosine (DIT), respectively (Figure 2.2). This and the following reactions are dependent on thyroid peroxidase in the presence of hydrogen peroxide -both located at the apical membrane. As MIT couples to DIT it produces tri-iodothyronine (3,5,3`-T3), whereas two DIT molecules form tetra-iodothyronine (T4), or thyroxine. These two molecules are the two thyroid hormones. Small amounts of the inactive reverse T3 (3,3`,5`- T3) is also synthesised (31).
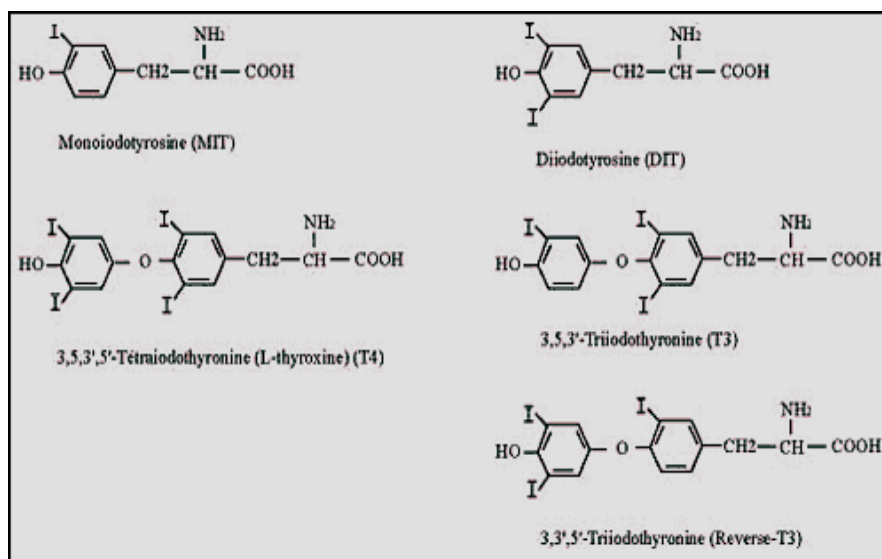
Figure 2.2: Structural formula of thyroid hormones and precursor compounds (23).

The newly formed iodothyroglobulin forms one of the most important constituents of the colloid material, present in the follicle of the thyroid unit. The other synthetic reaction, that is closely linked to organification, is a coupling reaction, where

iodotyrosine molecules are coupled together. If two di-iodotyrosine molecules couple together, the result is the formation of thyroxin (T4). If a di-iodotyrosine and a mono-iodotyrosine are coupled together, the result is the formation of tri-iodothyronine (T3). (Figure 2.3).
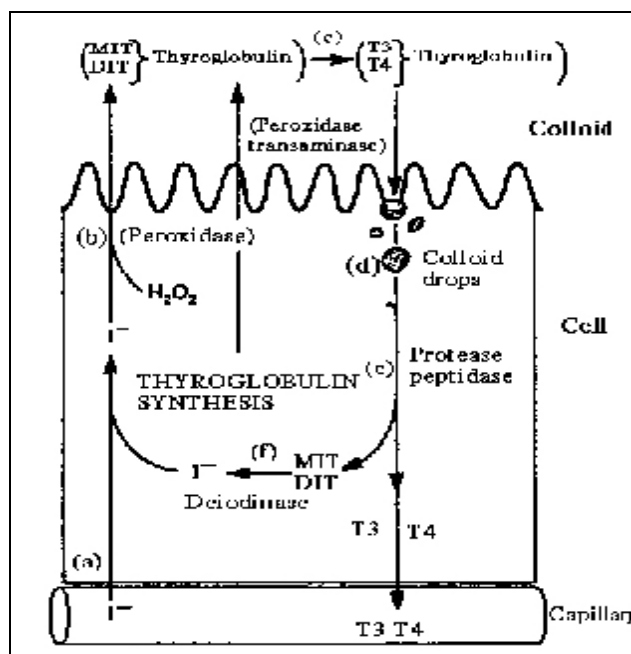
Figure 2.3: Synthesis of thyroid hormones

Iodide is organified in the tyrosyl residues of Tg in a reaction catalyzed by TPO, in the presence of H_2O_2, Tg contains MIT, DIT, T_3, and T_4 and is stored in colloid until T_3 and T_4 need to be released into the blood (32).

From the perspective of the formation of thyroid hormone, the major coupling reaction is the di-iodotyrosine coupling to produce T4. Although T3 is more biologically active than T4, the major production of T3 actually occurs outside of the thyroid gland. The majority of T3 is produced by peripheral conversion from T4 in a deiodination reaction involving a specific enzyme which removes one iodine from the outer ring of T4. The T3 and T4 released from the thyroid by proteolysis reach the bloodstream where they are bound to thyroid hormone binding proteins. The major thyroid hormone binding protein is thyroxin binding globulin (TBG) which accounts for about 75% of the bound hormone. In order to attain normal levels of thyroid hormone synthesis, an adequate supply of iodine is essential. The recommended minimum intake of iodine is 150 micrograms a day. Intake of less than 50

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micrograms a day is associated with goiter. High iodine levels inhibit iodide oxidation and organification. Additionally, iodine excess inhibits thyroglobulin proteolysis (33).

Cells of the brain are a major target for the thyroid hormones T3 and T4. Thyroid hormones play a particularly crucial role in brain maturation during fetal development. A transport protein called organic anion transporter (OATP1C1) has been identified that seems to be important for T4 transport across the blood brain barrier. A second transport protein called monocarboxylate transporter 8 (MCT8) is important for T3 transport across brain cell membranes (34).

2.5 Mechanisms of thyroid hormone action

As illustrated in Figure 2.4.   circulating free TH enters the cell by either passive diffusion or other. TH then enters the nucleus, where it binds to the nuclear thyroid-hormone receptor (TR). TR is a ligand-regulated transcription factor that is intimately associated with chromatin, and also associates with other nuclear proteins to form heterodimers. These in turn are bound to target DNAs known as TH-response elements (TREs). The formation of a liganded TR/DNA complex leads to activation of its associated gene, and to consequentchanges in messenger RNA (mRNA) and protein. Thus, the central role of TR in the nuclear action of TH is evident.
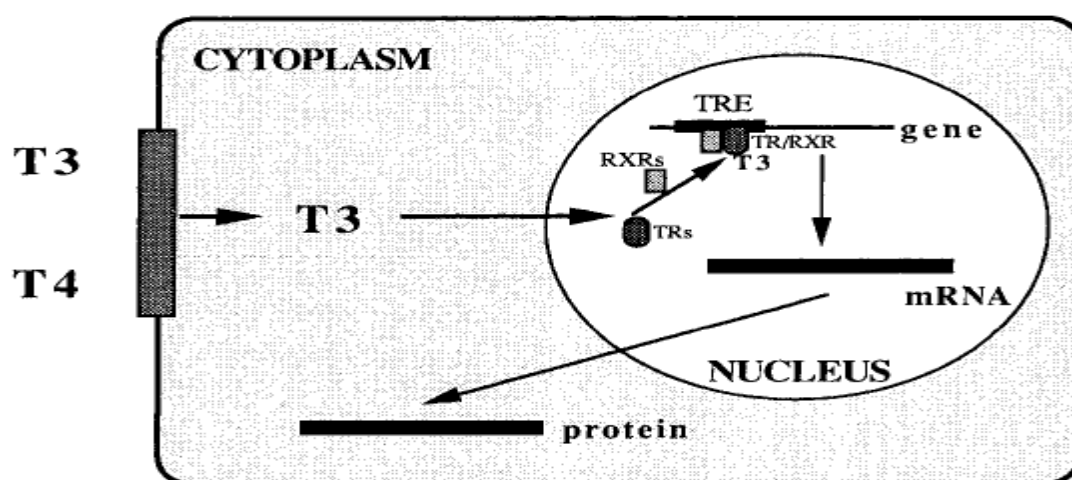
Figure 2.4: TH action at the nuclear level.

Thyroid hormone (T4 and T3; TH) exerts numerous effects on the cell. Whereas many of its actions involve regulation of gene expression, thyroid hormone may also act at the plasma membrane, cytoplasm, mitochondrion, and other non-nuclear sites. T3 and T4 may enter the cell by passive diffusion or other poorly defined pathways. In addition, T4 may be deiodinated to more active T3 by iodothyronine 5′-deiodinases. Furthermore, T3 may be subjected to degradation within the cell. T3 then enters the nucleus to bind to the thyroid hormone receptor (TR). The TR, in collaboration with a number of other nuclear proteins including the RXRs, form heterodimers that are bound to target DNA sites known as thyroid hormone-response elements (TRE). The liganded TR/RXR/TRE complex initiates alterations in gene expression among genes containing such TREs, and these alterations in turn alter their corresponding mRNA and protein levels.(35,36).

2.5.1 THYROID HORMONE RECEPTORS

TRs are ligand-regulated transcription factors that are members of the steroid hormone receptor superfamily. TRs are encoded by a protooncogene, *c-erb*A, and are represented by two genomic loci (α and β), located on human chromosomes 17 and 3, respectively (37,38). The T3 response element (TRE) is composed of repeated DNA sequences with different configurations. Although TRs can bind to TREs as monomers or homodimers, the major form of TR bound to the TRE is the heterodimer with retinoid X receptor (RXR) (39). Each TR contains a DNA-binding domain (DBD) with zinc finger motifs, and a ligand binding domain (LBD). Ligand binding causes major conformational changes in the LBD, that allow TRs to discriminate between coactivators and corepressors(40). The ability to bind specific sequences in target genes is crucial for TR function. The consensus sequence recognized by nuclear receptors often contains a hexamer AGGTCA known as the half site. Functional and efficient binding requires two of the half-site sequences with different configurations.(41,42). TR predominantly bind DNA response elements as heterodimers with RXRs Heterodimer formation is thought to enhance DNA-binding affinity as well as provide target gene specificity, determined by the spacing between two half sites(43).

2.5.2 MECHANISMS OF TRANSCRIPTIONAL REGULATION

As a transcriptional factor, a key function of the TR is to regulate the target gene expression in response to multiple signaling pathways. TR constitutively bind to DNA response elements in the absence and presence of the ligand. Unliganded TR represses the basal transcription. Ligand binding causes derepression and enhances transcriptional activation. Thus the biological significance of repression is to turn off target genes in the absence of hormone and to increase the magnitude of transcriptional activation by hormone ligand. A group of cofactor proteins (coactivators and corepressors) mediate repression and activation (Figure2.5).
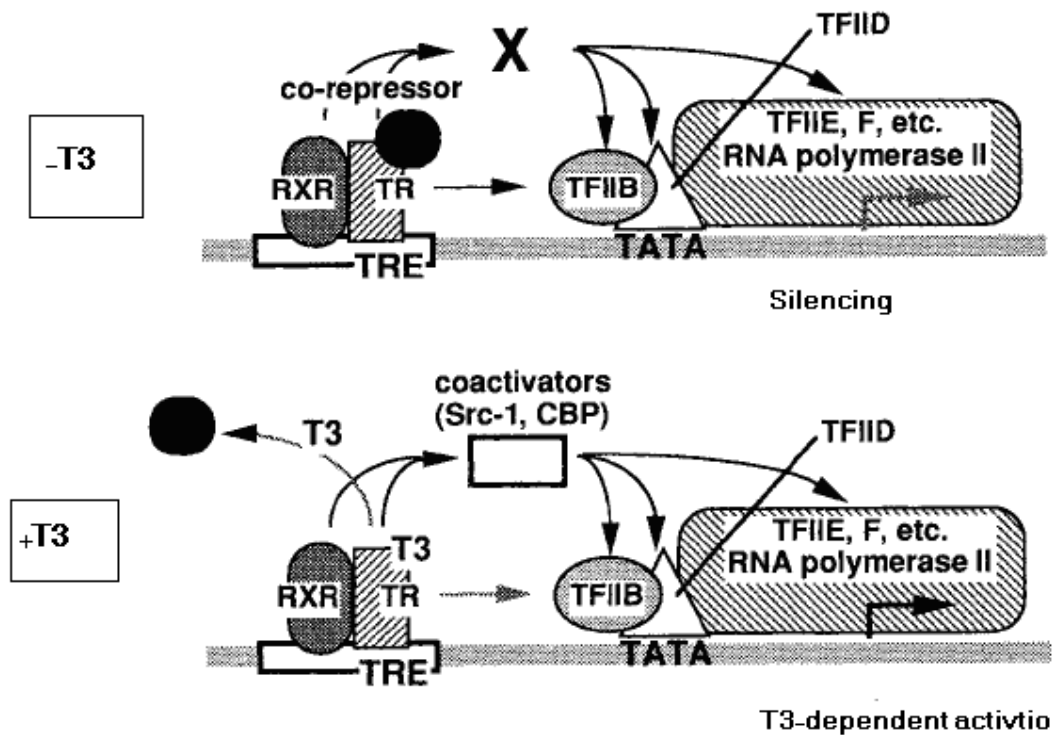
Figure 2.5: Molecular mechanisms of TH action

This diagram illustrates the factors involved in TH action on a TRE in the absence (−T3 and presence (+T3) of TH. In the −T3 state, TR_RXR heterodimer is bound to a TRE that is, in turn, associated with a corepressor. The presence of the corepressor in this configuration results in silencing of the associated gene. The direct interaction of unliganded TR with the basal transcription factor, TFIIB, may also participate in this silencing function. The addition of T3 results in dissociation of the corepressor and subsequent association with putative coactivators such as SRC-1 and CBP to result in activation of the basal transcription machinery (TFIIB, TFIID, TFIIE and F, RNA polymerase II, etc.) and stimulation of the associated gene by T3.

Cofactors alone cannot bind DNA but instead they directly interact with DNA-bound nuclear receptors, as a result of which they are recruited to the proximity of the target gene promoter region and affect the rate of transcription. A higher levelA higher level of transcriptional regulation is provided by a change of chromatin structure. Open chromatin is thought to facilitate the assembly of basal transcriptional machinery and increase the transcription rate. In contrast, a highly condensed chromatin blocks the entry of TATA-binding protein and leads to transcriptional repression. Chromatin structure can be greatly affected by acetylation of histones in the nucleosome octamer. Hyperacetylation of histones loosens the interaction between DNA and nucleosome opposes the structural change of nucleosomes brought by histone acetylation by reducing the net positive charge. Conversely, histone deacetylation Both histone acetyltransferase and histone deacetylase activities are functionally associated with coactivators and corepressors, respectively, thus providing an enzymatic link to the activation and repression by nuclear receptors.(44)

2.6 Regulation of thyroid hormones

The production of T4 and T3 is regulated by TSH, released by the anterior pituitary that is in turn released as a result of thyrotropin-releasing hormone (TRH) released by the hypothalamus. As shown in Figure 2.4, the thyroid and thyrotropes form a negative feedback loop: TSH production is suppressed when the T4 levels are high, and vice versa. The TSH production itself is modulated by TRH, which is produced by the hypothalamus and secreted at an increased rate in situations such as cold (in which an accelerated metabolism would generate more heat). TSH production is blunted by somatostatin (SRIH), rising levels of glucocorticoids and sex hormones (estrogen and testosterone), and excessively high blood iodide concentration (45).

By a negative feedback mechanism, increased levels of free thyroid hormones (T4 and T3) inhibit TSH secretion from the pituitary, whereas decreased levels of T4 and T3 cause an increase in TSH release from the pituitary. TSH secretion is also

influenced by TRH synthesized in the hypothalamus. TRH causes release of TSH (Figure 2.4).
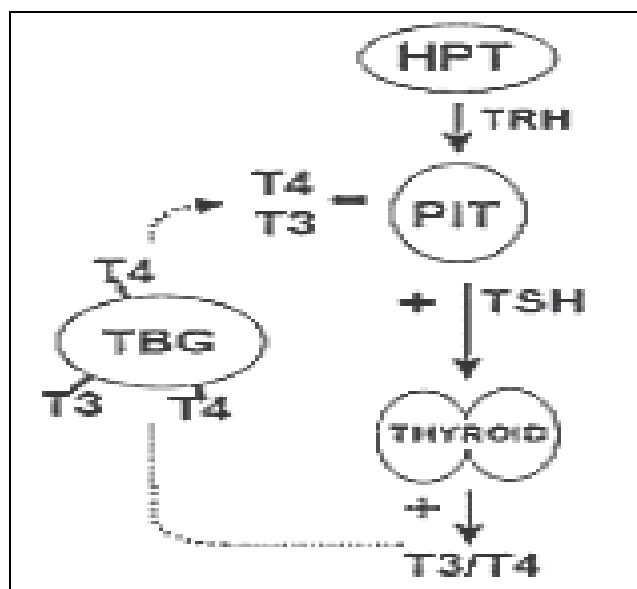
Figure 2.6: Regulation of T3 and T4 secretion (46)

HPT: hypothalamus, PIT: pituitary, TRH: thyrotropin-releasing hormone, TSH: Thyroid stimulating hormone, TBG: thyroid binding globulin, T4:thyroxine, T3:triidothyronine.

2.7 Thyroid stimulating hormone (TSH)

TSH stimulates the thyroid gland to secrete the hormones T4 and T3. TSH is a glycoprotein which consists of two subunits, the alpha and the beta subunit. The alpha (α) subunit is identical to that of hCG, luteinizing hormone (LH), follicle-stimulating hormone (FSH). The β (beta) subunit (TSHB) is unique to TSH, and therefore determines its function. TSH production is controlled by a TRH, which is manufactured in the hypothalamus and transported to the anterior pituitary gland via the superior hypophyseal artery, where it increases TSH production and release. Somatostatin is also produced by the hypothalamus, and has an opposite effect on the pituitary production of TSH, decreasing or inhibiting its release. The level of thyroid hormones (T3 and T4) in the blood have an effect on the pituitary release of TSH; When the levels of T3 and T4 are low, the production of TSH is increased and conversely, when levels of T3 and T4 are high, then TSH production is decreased (47).

This effect creates a regulatory negative feedback loop. Determining TSH in the serum is a basic search procedure in the diagnosis of the thyroid gland's function. Its regulation is based on feedback, however, during pregnancy there are also other

mechanisms taking place (mainly suppression of TSH) presumably due to the thyroid-stimulating activity of hCG early in pregnancy when hCG levels are the highest (48). By using the classic reference interval for serum TSH, one might misdiagnose as healthy women who already have a slight TSH elevation and, conversely, one might suspect hyperthyroidism in normal women who have a lowered serum TSH value (49).

2.8 Thyroid diseases

2.8.1 Hypothyroidism

Hypothyroidism is almost due to disease within thyroid gland that causes a decrease in the production of thyroid hormones. The most common causes of this disorder are shown in Table 2.1.

Table 2.1. Etiology of hypothyroidism (50-52)

Hashimoto disease
Postthyroid ablation/removal
Iodine deficiency
Primary atrophic hypothyroidism
Infiltrative disease
TSH-dependent hypothyroidism

Women are more predisposed hyopthyroidism than men (53). Hypothyroidism during fetal development or early infancy results in cretinism (congenital hypothyridism) which causes respiratory difficulties, persistent jaundice, and hoarse crying, stunted growth (dwarfism), bone and muscle dystrophy, and mental deficiency in older children, and the incidence is 3 times more in girls than in boys. Infants not treated within the first 3 months or children within two years suffer irreversible mental retardation (54).

2.8.1.1 Symptoms of hypothyroidism

The signs of hypothyroidism are depending on the organ which is affected. As thyroid begins to fail, slight enlargement of thyroid gland (goiter), appearing as a lump or swelling, then the patient may begin to feel tired. Some hair loss may be

noticed. Then ingernails become thickened, dry, and brittle. Hypothyroidism becomes more severe, changes may occur in the tissues beneath skin that lead to a characteristic swollen appearance known as myxedema. This is often particularly apparent around face and eyes (55). Circulation is affected and heart rate slows. Since intestinal activity slows down, patient may become constipated. A few pounds of weight gain may occur. Muscles may become painful with leg cramps. Nervous system may be affected in several ways. Some memory loss may be noticed, decreased ability to think, and depression. Some patients suffer loss of balance and difficulty in walking. In women, changes in reproductive system may cause longer, heavier, and more frequent menstruation. Their ovaries may stop producing an egg each month, and, if so, it may be difficult to get pregnant. So in hypothyroid, many of the affected bodily functions simply slow down (56).

2.8.1.2 Diagnosis of hypothyroidism

Appropriate laboratory evaluation is critical to establish the diagnosis and cause of hypothyroidism in the most cost-effective way. The most valuable test is a sensitive measurement of TSH level. A TSH assay should always be used as the primary test to establish the diagnosis of primary hypothyroidism. Additional tests may include the following:

- Free T4 estimate**:** determination of FT4 is by watching the amount of biologically active hormone which is available to the a pregnant woman (as well as the fetus), and is not affected by the concentration of binding proteins. Its concentration during pregnancy is partly affected by both the inflow of iodine and the duration of the pregnancy. Some consider it even more informative than TSH during pregnancy (14). The fetus is completely dependent upon thyroxin produced by the mother during the first trimester. Even a small unnoticed malfunction of the mother's thyroid gland, which doesn't necessarily endanger the course of the pregnancy, can affect the psychomotor development of the child (57).
- Thyroid autoantibodies—anti-thyroid peroxidase and antithyroglobulin autoantibodies.
- Thyroid scan, ultrasonography, or both (if necessary to evaluate suspicious structural thyroid abnormalities (58).

2.8.2 Subclinical hypothyroidism

The term subclinical hypothyroidism is used for patients who have mildly increased levels of serum TSH but normal thyroid hormone T4 and T3 levels (59). An increase in serum TSH concentration is an early and sensitive indicator of decreased thyroid reserve. However, the interpretation of thyroid function tests in the pediatric age range is more difficult than in adults. Although normal ranges have been defined for all age groups from birth to maturity, significant discrepancies still persist between different laboratories. It is therefore important that each laboratory determines its own normal values and the results must always be interpreted cautiously (60). It is clear that thyroxine therapy is indicated in overt hypothyroidism and uniform agreement exists that it is also indicated for patients whose TSH levels are permanently increased above 10 mIU/L. For TSH levels between 5 – 10 mIU/L, therapy for these milder forms is controversial. In clinical practice some doctors treat all such patients while others choose to reassess the thyroid function in 3-6 months to find out if the thyroid abnormality is transient. Subclinical hypothyroidism is one spectrum of autoimmune thyroiditis, the clinical course is variable and spontaneous remission may occur in adolescence (61). Adults with subclinical hypothyroidism, especially with thyroid antibodies have been shown to result in overt hypothyroidism with a rate of 5-20 % per year. on the contrary, a very low risk for overt hypothyroidism has been shown in children and adolescents during a 5 year follow up (62).

Children and adolescents with type 1 diabetes, with juvenile arthritis and with epilepsy who are treated with valproate or carbamazepine are in risk for subclinical hypothyroidism and their thyroid function should be followed regularly (63). Early detection of subclinical hypothyroidism with treatment of thyroxine has shown to improve growth and metabolic control in type 1 diabetics (64). Increased TSH-levels with mildly increased thyroid hormone levels have also been found in up to 15 % of obese children and adolescents (65). There is, however, no need to treat these patients, hyperthyrotropinemia is reversible after weight loss (66). It has been suggested recently that subclinical hypothyroidism is a cardiovascular risk factor in adults and physiological thyroxine replacement has a beneficial effect on low density lipoprotein cholesterol levels (67).

2.8.3 Hyperthyroidism

Hyperthyroidism is the consequence of excessive thyroid hormone action. The causes of hyperthyroidism include the followings (Table 2.2):

Table 2.2: Etiology of hyperthyroidism (68,69)

- Toxic diffuse goiter (Graves' disease)
- Toxic adenoma
- Toxic multinodular goiter (Plummer's disease)
- Painful subacute thyroiditis
- Silent thyroiditis, including lymphocytic and postpartum variations
- Iodine-induced hyperthyroidism (for example, related to amiodarone therapy)
- Excessive pituitary TSH or trophoblastic disease
- Excessive ingestion of thyroid hormone

Globaly every year, 350.000 people develop some kind of hyperthyroidism, and it is eight to ten times more common in women than in men (70).

2.8.3.1 Symptoms of hyperthyroidism

The spectrum of possible signs and symptoms associated with the various causes of hyperthyroidism includes nervousness and irritability, Palpitations and tachycardia, Heat intolerance or increased sweating, tremor, weight loss or gain, alterations in appetite, diarrhea Sudden paralysis, Exertional intolerance and dyspnea, menstrual disturbance (decreased flow), impaired fertility, mental disturbances, sleep disturbances (including insomnia), Changes in vision, photophobia, eye irritation, diplopia, Fatigue and muscle weakness, thyroid enlargement and Pretibial myxedema (in patients with Graves' disease). A patient with hyperthyroidism need not have all these symptoms **(68, 69)**

2.8.3.2 Diagnosis of hyperthyroidism

❖ A comprehensive history should be elicited, and a thorough physical examination should be performed, including the followings:

- Weight and blood pressure

- Pulse rate and cardiac rhythm

- Thyroid palpation and auscultation (to determine thyroid size, nodularity, and vascularity)

- Neuromuscular examination

- Eye examination (to detect evidence of exophthalmos or ophthalmopathy)

- Dermatologic examination

- Cardiovascular examination

- Lymphatic examination (nodes and spleen)

❖ Laboratory Evaluation: The development of sensitive TSH assays has considerably facilitated the diagnosis of hyperthyroidism. The sensitive TSH test refers to a TSH assay with a functional sensitivity of 0.02 or less. Hyperthyroidism of any cause results in a lower-than normal TSH level (suppressed TSH). The sensitive TSH assay is the single best screening test for hyperthyroidism. Other laboratory and isotope tests may include the following(70):

- T4 or free T4

- Triiodothyronine (T3) radioimmunoassay (RIA) or free T3

- Thyroid autoantibodies, including TSH receptor antibodies

- Thyroid-stimulating immunoglobulins (TSI)

- Radioactive iodine uptake

2.8.4 Sub clinical hyperthyroidism

Subclinical hyperthyroidism is an entity that is being increasingly recognized. This may be both due to the aging of the population and the development of more sensitive TSH. Subclinical hyperthyroidism is defined as the combination of a supressed, usually undetectable serum TSH concentration, and normal serum free T3 and T4 concentrations. The TSH value is measured by an assay with a threshold of

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detection that is 0.3 mU/L or less (71). Patients with subclinical hyperthyroidism are usually euthyroid, but symptoms or signs of thyrotoxicosis such as malaise, tachycardia, nervousness and anxiety may be present. In elderly, atrial fibrillation may be the initial manifestation. The sensitivity of the pituitary gland to respond to minor elevations in serum or tissue T3 and T4 levels is the main pathophysiological mechanism of subclinical hyperthyroidism. Abnormal TSH levels may remain for years without clinical symptoms of overt hyperthyroidism. The rate of progression of subclinical hyperthyroidism to overt disease is at least 1 to 3 percent per year (72). A suppression of TSH level may be due to nonthyroidal illness, steroid or dopamine administration, or pituitary dysfunction; so, these conditions must be excluded. According to its cause, subclinical hyperthyroidism can be classified as endogenous and exogenous. The endogenous causes of subclinical hyperthyroidism include multinodular goiter, Graves' disease (early), solitary auto-nomous adenoma, thyroiditis and other causes of hyperthyroidism e.g., trophoblastic tumors. The exogenous causes of subclinical hyperthyroidism include treatment with evothyroxine, exogenous iodine exposure such as recent administration of radio contrast material. A 24-hour radioactive iodine uptake will generally be elevated in patients with Graves' disease, multinodular goiter, and solitary autonomous nodule; but will be decreased in patients in the hyperthyroid phase of subacute, silent, or postpartum thyroiditis and in patients taking excess exogenous thyroid hormone. In clinical examination, thyroid gland may be enlarged in some patients, but in most patients it is usually normal in size (73).

2.9 Risk factors for thyroid disease: autoimmunity and other conditions

Several risk factors predispose women to hypothyroidism during pregnancy, including autoimmune thyroid disease (AITD), type 1 diabetes mellitus, other endocrine deficiencies, Down syndrome, Turner syndrome, thalassaemia major, thyroid ablation. and who are treated with pituitary surgery or irradiation, head and neck irradiation, treatment of growth hormone deficiency, cytotoxic therapy, lithium, interferon α, interferon β, and therapeutic monoclonal antibodies. Patients with a family or personal history of thyroid disease, goiter, history of spontaneous abortion, Positive thyroid peroxidase antibody, origin from areas of endemic iodine deficiency, Previous thyroid disease or surgery, or any symptoms suggesting hypothyroidism, are at higher risk for hypothyroidism. Recent studies have suggested that AITD

independent of hypothyroidism, may have adverse effects, which include increased risk of miscarriages and recurrent miscarriages, fetal death, and possible effects on childhood cognition, and postpartum depression (74, 75).

2.10 Maternal thyroid physiology

The high circulating estrogen levels during pregnancy change the pattern of glycosylation of TBG at the time of hepatic synthesis, leading to a longer plasma half-life and, consequently, an increase in the plasma TBG concentration(76) This lead to increased serum T_4-binding globulin and T_4 concentrations (77 , 50, 78). Although a transient decrease in serum free T_4, followed by a rise in TSH to a new equilibrium, may occur (79), this is usually not appreciated with routine thyroid testing. A high circulating hCG level in the first trimester leads to hCG cross-reactivity with the TSH receptor, prompting a temporary increase in free T_4 and partial suppression of TSH. The final physiologic change results from placental deiodination of maternal T_4, which increases T_4 turnover. In normal pregnant women, the thyroid gland maintains euthyroidism with only minor fluctuations in serum T_4 and TSH. However, in women with limited thyroid reserve, due to thyroid autoimmunity or iodine deficiency, hypothyroidism can develop. Fetal thyroid ontogeny begins at 10–12 weeks gestation and is not complete until delivery; T_4 is not secreted until 18–20 weeks (77, 78). T_4 is critical for many aspects of brain development including neurogenesis, neuronal migration, axon and dendrite formation, myelination, synaptogenesis, and neurotransmitter regulation (79). Although these requirements evolve over months (80), an especially critical time is the second trimester (81).

2.11 Fetal thyroid physiology and the effect of maternal thyroid status

Fetal thyroid function occurs from the end of the first trimester. Prior to that, there is evidence that normal development of the fetal brain is dependent upon maternally derived T4, which is converted intracellularly to T3. Such T4 has been detected from 5-8 weeks' gestation and by 11 weeks it is at 100 times greater concentration than in the maternal circulation. Maternal hyothyroxinaemia at this stage may have adverse effects on subsequent fetal brain development. Fetal FT4 and total T4 reach adult levels by 36 weeks gestation, fetal TSH is greater than adult TSH and fetal T3 remains low. The relatively high levels of T4 allow intracellular conversion to T3 in the fetal brain. When fetal thyroid dysfunction occurs, maternally derived T4 becomes

essential to allow normal neurological development. Placental perfusion studies have demonstrated that, in normal pregnancy at term, very little (0.008%) maternal T4 crosses to the fetal side; inhibition of placental deiodination of T4 enhances transfer 2700-fold, so that fetal levels reach 30% of maternal concentrations. In pregnancy complicated by fetal thyroid dysfunction, deiodinase III is inhibited, allowing additional transfer of T4 to the fetus, reduced fetal peripheral deiodination of T4 and enhanced intracellular activation to T3 in the fetal brain, so protecting it from permanent damage.(82)

2.12 Regulation of thyroid function during normal pregnancy

2.12.1 Increase in thyroid-binding globulin

In conditions with TBG excess, such as pregnancy, the proportion of circulating T4 carried by TBG is even greater, in excess of 75%, which indicates that TBG represents the major thyroid hormone transport protein in pregnancy (83). During pregnancy the respective affinities of the three binding proteins for their hormonal ligands are not significantly modified, and the circulating levels of both serum albumin and transthyretin remain stable, with only a slight tendency to decrease near the end of gestation, mainly as a result of passive hemodilution due to the increased vascular pool (84). Thus, the major change for thyroid hormone-binding proteins involves the marked and rapid increase in serum TBG levels as a result of estrogen stimulation. Compared with preconception concentrations (average 15–16 mg/liter), serum TBG begins to increase in pregnancy after a few weeks and reaches a plateau around midgestation, 2.5-fold higher than the initial value, between 30–40 mg/liter (85, 86, 87). The mechanism for this increase in TBG involves both an increase in hepatic synthesis of TBG and an estrogen-induced increase in sialylation, which increases the half-life of TBG from 15 min to 3 days for fully sialylated. TBG that lead to lowered free T4 concentrations, which results in elevated TSH secretion by the pituitary and, consequently, enhanced production and secretion of thyroid hormones. The net effect of elevated TBG synthesis is to force a new equilibrium between free and bound thyroid hormones and thus a significant increase in total T4 and T3 levels. The increased demand for thyroid hormones is reached by about 20 weeks of gestation and persists until term (88).

2.12.2 Increases in total T4 and T3

In pregnancy, the alterations in total TH levels are the direct consequence of the marked increase in serum TBG: total T4 and T3 levels increase significantly during the first half of gestation. Levels of serum T4 rise sharply between 6 and 12 weeks, progress more slowly thereafter, and stabilize around midgestation, for serum T3, the rise is more progressive (89). Both total T4 and T3 reach their plateau values by 20 weeks and are maintained until term because of the 20-fold greater affinity of TBG for T4 compared with T3, changes in T4 levels follow the changes in TBG more closely. It can be expected therefore that the T3/T4 molar ratio should remain essentially unaltered during pregnancy (90,91). The etiology of this increase in total circulating thyroid hormones involves, primarily, increased concentrations of plasma TBG. Another proposed mechanism for this increase in total thyroid hormone concentrations is production of type III deiodinase from the placenta. This enzyme, which converts T4 to reverse T3, and T3 to diiodotyrosine (T2), has extremely high activity during fetal life. Increased demand for T4 and T3 has been suggested to increase production of these hormones with, ultimately, increased concentrations in the circulation. The increase in T4 and T3 concentrations is less than would be expected by the increase in TBG as a relative hypothyroxinemia (92). On average, pregnant women had lower free hormone concentrations at term than non pregnant women. Other studies have confirmed that serum free T4 and T3 are ~25% lower in women at delivery than non pregnant subjects. However, most pregnant women (>78%) remain within the same reference interval as non pregnant women (93).

2.12.3 Thyroid stimulation by hCG

HCG is a member of the glycoprotein hormone family that is composed of a common α-subunit and a hormone-specific β-subunit, non-covalently associated. The α-subunit of hCG consists of a polypeptide chain of 92 amino acid residues containing two N-linked oligosaccharide side-chains. The hCG β-subunit consists of 145 residues with two N-linked and four O-linked oligosaccharide side-chains. The TSH β-subunit is composed of 112 residues and one N-linked oligosaccharide. The β-subunits of both possess 12 half-cysteine residues at highly conserved positions. Three disulfide bonds form a cystine knot structure, which is identical in both TSH and hCG and is essential for binding to their receptor (LH and hCG bind to the same receptor). The β-

subunit has strong homology with LH, but it also has a C-terminal tail peptide that contains 4 O-linked oligosaccharide units that contribute substantially to its molecular weight (94).

A single gene on chromosome 6 encodes for the common α-subunit, while the genes that encode for the β-subunits are in a cluster on chromosome 19, with seven genes (but only three actively transcribed) coding for βhCG (95, 96, 97). Serum hCG rises exponentially during the first trimester of pregnancy, peaking at 10 to 12 weeks of pregnancy (98). During a normal pregnancy, the direct stimulatory effect of hCG on the thyroid induces a small and transient increase in free thyroxine levels near the end of the 1st trimester (peak circulating hCG) and in turn a partial TSH suppression. In bioassays, hCG is only about $1/10^4$ as potent as TSH during normal pregnancy. This weak thyrotropic activity explains why, in normal conditions, the effects of hCG remain largely unnoticed and thyroid function tests unaltered (4). When hCG is at its greatest concentration, serum TSH concentrations drop, creating the inverse image of hCG. In most pregnancies, this decrease in TSH remains within the health-related reference interval. Under pathological conditions in which hCG concentrations are markedly increased for extended periods, significant hCG-induced thyroid stimulation can occur, decreasing TSH and increasing free hormone concentrations (99).

2.12.4 Increase in renal iodide clearance

Iodine is available from maternal circulation to the fetal-placental unit. The extent of iodine passage from mother to fetus has not yet been precisely established. At gestation, the fetal thyroid gland has already started to produce thyroid hormones that are indispensable for an adequate development of the fetus (100). The main changes in thyroid function associated with pregnancy are related to increased hormone requirements, which begin in the first trimester of gestation. Increased hormone requirements can only be met by proportional increased hormone production, directly depending upon the availability of iodine in the diet. When iodine nutrition levels are sufficient, physiological adaptation takes place. Furthermore, iodine deficiency may be associated with alterations of the neuropsychointellectual outcome in the progeny, and the risk for an abnormal development of the progeny is further enhanced because both the mother and offspring are exposed to the deficiency not only during the entirety of gestation but also during the postnantal period (101).

In pregnancy, the renal clearance of iodide increases substantially because of an increased glomerular filtration rate. The iodide loss lowers the circulating concentrations of iodide and produces a compensatory increase in thyroidal iodide clearance. In areas of the world where iodine intake is sufficient, such as the US, the iodide losses in the urine are not clinically important. In other areas of the world, however, iodine deficiency during pregnancy can lead to hypothyroidism and goiter and poses a serious public health issue. Approximately 500 million people live in areas of overt iodine deficiency. In the non pregnant condition, adequate iodine intake is estimated to be 100–150 μg/day. The World Health Organization recommends that during pregnancy, iodine intake be increased to at least 200 μg/day (102).

2.12.5 Increase in serum thyroglobulin

Thyroglobulin frequently is increased during pregnancy, reflecting the increased activity of the thyroid gland during pregnancy. The increase in thyroglobulin can be seen as early as the first trimester, but it is more pronounced in the latter part of pregnancy. Increased serum thyroglobulin concentrations are also associated with an increase in thyroid volume. Despite this, goiter, as defined by thyroid volume >23 mL, occurs in only 5–15% of women at term. This low incidence is likely attributable to adequate intake of dietary iodine (103). A summary of changes in the thyroid tests during pregnancy are given in Table 2.3.

Table2.3 A summary of changes in thyroid tests during pregnancy.(6)

Thyroid function tests during pregnancy.	
Physiologic change	**Resulting change in thyroid activity**
↑ serum estrogens	↑ serum TBG
↑ serum TBG	↑ demand for T_4 and T_3
	↑ in total T_4 and T_3
↑ hCG	↓ TSH (in reference range unless hCG >50 000 IU/L)
	↑ fT_4 (in reference range unless hCG >50 000 IU/L)
↑ iodine clearance	↑ in dietary requirement for I^-
	↓ in hormone production in I^--deficient areas
	↑ goiter in I^--deficient areas
↑ type III deiodinase	↑ T_4 and T_3 degradation
	↑ demand for T_4 and T_3
↑ demand for T_4 and T_3	↑ serum thyroglobulin
	↑ thyroid volume
	↑ goiter in I^--deficient areas

↓: Decrease
↑: Increase

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2.13 Hyperthyroidism during pregnancy

The incidence of hyperthyroidism in pregnant women has been estimated at 0.2% and is mostly caused by Graves' disease.(52) Most women have symptoms before pregnancy, but some will demonstrate symptoms for the first time during pregnancy. The most common causes are shown in Table 2.4.

Table (2.4): Etiology of hyperthyroidism in pregnancy (51, 104)

Graves disease (85–90% of all cases)
Sub-acute thyroiditis
Toxic multinodular goiter
Toxic adenoma
TSH-dependent thyrotoxicosis
Exogenous T3 or T4
Iodine-induced hyperthyroidism
Pregnancy-specific associations
Hyperemesis gravidarum
Hydatidiform mole

Maternal complications include miscarriage, abruptio placenta, and preterm delivery. Congestive heart failure and thyroid storm may also occur and the risk of preeclampsia is significantly higher in women with poorly controlled hyperthyroidism.

2.14 ypothyroidism during pregnancy

The incidence of hypothyroidism in pregnant women has been estimated to be 0.3–0.7% *(50)*. There is a known association between hypothyroidism and decreased fertility *(105–107)*. For this reason, the frequency of hypothyroidism in pregnancy is actually lower than the 0.6–1.4% frequency in the general population *(50)*. Causes of hypothyroidism during pregnancy are listed in Table(2.5).

Table 2.5: Etiology of hypothyroidism in pregnancy(50, 51, 108)

Hashimoto disease

Postthyroid ablation/removal

Iodine deficiency

Primary atrophic hypothyroidism

Infiltrative disease (e.g., sarcoid, amyloidosis)

TSH-dependent hypothyroidism

2.15 Related studies

To evaluate the incidence of thyroid function disorder in Singaporean 184 unselected pregnant women who were in their 8th to 14 th weeks of pregnancy were tested for Serum F T4, F T3, TSH. Two subjects (1·1%) were found to have Graves' disease and elevated free T4, free T3 and suppressed TSH were seen in 14·8%, 3·3% and 33·0% of the remaining 182 pregnant women, respectively. 11·0% of cases had gestational thyrotoxicosis (GT) defined as elevated free T4 (> 19·1 pmol/l), suppressed TSH (< 0·36 mIU/l). The prevalence of GT was significantly higher in patients tested at 8–11 weeks compared to those evaluated at 12–14 weeks (14·4% *vs.* 4·7%, *P* < 0·05). and free T4 (*P* = 0·02) levels were higher and TSH levels (*P* = 0·01) lower in patients tested at 8–11 weeks.(109)

To evaluate serum levels of TSH in 124 pregnant women. The women were apparently normal, healthy young primigravidas. consecutively attending the antenatal clinic were included in the study. Mean TSH levels was 1.20 microlU/ ml. Three asymptomatic pregnant women (2.5%) were found to have abnormal TSH. the values with normal T3 and T4 levels where normal obstetric outcome was good. (110)

The incidence of thyroid disorder in Tunisian determined TSH and TPO-Ab in 1519 pregnant women aged 17 to 47 years. Thyroid disorder was defined as hyperthyroidism (TSH≤0.10 mIU/L) or hypothyroidism (TSH >4.5 mIU/L), and/or positive TPOAb (>12 IU/L). Thyroid disorders were observed in 147 pregnant women (9.7%). Positive TPO-Ab was noted in 99 women (6.5%), hypothyroidism in 48 thyroid disorders women (3.2%) and hyperthyroidism in 10 women (1.3%). (111)

A screening study for 4800 China women during the first half of pregnancy.. They were screened for thyrotropin, free thyroxine and thyroid peroxidase antibody. Two different series of reference intervals for TSH and FT4,were calculate, the gestational age-specific reference intervals (S1) and non-pregnant population reference intervals (S2) were used to diagnose thyroid dysfunction. The S2 of serum TSH was 0·3–4·8 mIU/L, FT4 was 10·3–24·5 pmol/L. hormone deficiency as the prevalence of subclinical hypothyroidism at 4, 8, and 12 weeks of gestation was

4.59%, 6.15%, 4.68%, respectively, and the prevalence of hypothyroxinaemia was 3.69%, 1.11%, 2.92%, respectively.(112)

A Study in Tabriz-Iran (2005) was carried out to find out alterations in thyroid function tests in each trimester in normal pregnant women as compared to non-pregnant women. A case-control study designed with 229 normal pregnant and 250 randomly selected non-pregnant healthy female controls. Age range in both groups was 16-40 years. Thyroid function tests carried out by measuring serum levels of TSH, FT4, and FT3. They found that mean FT4 was strongly decreased during the third trimester. Free T3 showed declining in the second and third trimesters. Mean TSH did not show significant difference in each trimester compared with non-pregnant women.. The thyroid function test for Non-pregnant women N=250 was FT4 pmol/L 14.40±10.46 , FT3 pmol/L 5.25±2.89 and TSH 1.93±1.04 µU/L. Pregnant Women First trimeste N=64 thyroid function test was FT4 pmol/L 14.90±4.67, FT3 pmol/L 6.84±2.02and TSH µU/L 1.71±1.38. (113) .

To study the influence of pregnancy on the results of free thyroxin measurement. Thirty-eight healthy pregnant women were enrolled in the study. Serial TSH, free thyroid hormone, total thyroid, HCG, and thyroid autoantibody levels. Data of 19 individuals were analyzed. An increase of total T3 and T4 levels was observed parallel with changes of TBG concentration during the first 4 months of gestation. Serum TSH time-curve showed a transient fall in the first trimester, thereafter it returned to the non-pregnant values. Curves of serum TSH and hCG created clear mirror images. Free T4 concentrations elevated in line with the HCG peak at the beginning of gestation, thereafter it clearly followed the course of serum TSH. Free T3 levels gradually decreased throughout pregnancy. The negative correlation between HCG and TSH levels, and the clear identity of the hCG +TSH and free T4 curves (114).

A Study was conducted in Geneva (2007) using surplus, de-identified serum specimens collected from pregnant women. A total of 2272 samples were included in the study. For the first trimester, mean maternal and median gestational age was 30.4 years and 7.6 weeks respectively. Of these women, 21.4% were positive for TPO-Ab

and/or Tg-Ab; 10.8% were TPO-Ab positive and 17.3% were Tg-Ab positive. TSH for First trimester (<6–12) weeks 0.8666(mU/l) for ≤6 weeks the mean was1.1946 while the mean was 0.7716 for>6-12 weeks. Manufacturer's non-pregnant reference interval is 0.35–4.94 mIU/l. Free T4 (pmol/l) First trimester (<6–12) weeks the mean was 13.96 for ≤6 weeks the mean was 13.68 and for >6-12 weeks the mean was 14.06 .Manufacturer's non-pregnant reference interval is 9.01–19.05 (pmol/l). Free T3 (pmol/l) First trimester(< 6–12) weeks the mean was 4.73 for≤6 weeks the mean was 4.63, And for >6-12 weeks the mean was 4.52 .Manufacturer's non-pregnant reference interval is 2.63–5.70 (pmol/l) (115).

In another study in India performed a case-control study designed with two groups of women: 75 normal pregnant women randomly selected from the first and 75 randomly selected non-pregnant healthy female controls. Thyroid function tests were carried out by measuring the serum levels of (TSH), (FT4), and (FT3). The results for TSH, FT4 and FT3 were 2.54 ± 1.32 (mIU/ml), 15.10 ± 11.56 (pmol/L) and 6.21 ± 3.10 (pmol/L) for non-pregnant women respectively. While the results of pregnant womens TSH 1.93 ± 1.53 (mIU/ml), FT4(14.93 ± 3.77) (pmol/L)and FT3 7.11 ± 2.32 (pmol/L). The mean FT4 levels in the first trimesters were non-significantly lower than that of the non-pregnant subjects. The pregnant groups' mean FT3 non-significantly higher than that of the non-pregnant subjects, the mean TSH levels of pregnant women were lower than the mean level of non pregnant but not significant. (116)

A studied of 118 healthy pregnant women living in an iodine-sufficient area. pregnant women with the mean age 30.9 ± 4.1 years in the first trimester. mean 11.2 ± 2.5 weeks of pregnancy), in the third trimester (mean 31.6 ± 1.7 weeks of pregnancy), All women were negative for thyroid autoantibodies .TSH was measured. Results: TSH concentration was significantly higher in the third trimester than in the first trimester (P = 0.007).(117)

To investigate the relationship between TSH and FT4, a study on 5520 women during the first trimester of pregnancy for serum TSH and FT4. Results: The reference

interval for TSH was determined to be 0.06–3.67 mU/l. The suppression of TSH was found in 2.93% of the women; a raised concentration of TSH had been found in 4.48% of the women. FT4 was determined only for women (n=697) with TSH lower than 0.1, for FT4 reference interval of 9.8–23.1 pmol/l for all populations. There were 30 (4.3%) women with FT4 under and 18 (2.5%) women with FT4 over the reference interval..(118)

In study in United States where a total of 10,990 patients had first- and second-trimester serum assayed for TSH, free T4), and antithyroglobulin and antithyroid peroxidase antibodies. Thyroid hypofunction was defined as 1) subclinical hypothyroidism: TSH levels above the 97.5th percentile and free T4 between the 2.5th and 97.5th percentiles or 2) hypothyroxinemia: TSH between the 2.5th and 97.5th percentiles and free T4 below the 2.5th percentile. Subclinical hypothyroidism was documented in 2.2% (240 of 10,990) in the firsttrimester . Hypothyroxinemia was documented in 2.1% (232 of 10,990) in the first Subclinical hypothyroidism was not associated with adverse outcomes. Hypothyroxinemia was associated with preterm labor(119)

MATERIALS AND METHODS

CHAPTER 3
MATERIALS AND METHODS

3.1 Study design

The present study is a cross Sectional

3.2 Target population

The target population was pregnant women in the first trimester from AL- Rimal Health Clinic, Gaza city.

3.3 Sampling and sample size

A total of 90 apparently healthy pregnant women aged 18-40 years in their 1–13th week of pregnancy were selected gestational ages were calculated based on the dates of their last menstrual period and findings from an ultrasound scan. The control group comprised 80 randomly selected non-pregnant healthy females of childbearing age.

3.4 Eligibility

3.4.1 Inclusion criteria

Healthy, pregnant women during the first trimester, gestational age 18-40 years and reside in Gaza city.

3.4.2 Exclusion criteria

Women who were diagnosed or treated for thyroid dysfunction, aged less than 18 years or more than 40 years and having serious diseases (including diabetes mellitus).

3.5 Ethical considerations

The researcher obtained the necessary approval to conduct the study from Helsinky committee (Annex 1). Coordination with the Ministry of Health was fulfilled (Annex 2). Informed consent was obtained from parents of all the participants. A full explanation about the purpose of the study, assurance about the confidentiality of the blood analysis, and the right to refuse or to participate (Annex 3) in the present study were given.

3.6 Questionnaire design

A face to face meeting between the researcher and subjects was the method of filling the questionnaire. The questionnaire includes personal data (e.g. age, address), number of miscarriages , number of pregnancies, thyroid problems, and receiving any medication and so on. (Annex 3).

3.7 Pilot study

Pilot study was done before the study started to evaluate the clarity of the questionnaire and to optimize the techniques. Ten pregnant women during the first trimester and a similar number of non pregnant women were interviewed, and blood samples were collected from them. At the end of the pilot study, a revision and modification was done on questionnaire as necessary.

3.8 Blood sampling and processing

Under quality control and safety procedure for sample collection, 5 ml venous blood sample was collected from 90 pregnant women during the first trimester in plain vaccutainer tubes. Also, 5ml venous blood samples were collected from 80 non pregnant women. Serum was separated from whole blood for all specimens using fine centrifugation at 3000 rpm for 15 min. Serum samples were sent to the lab within 2 hours of collection, for analysis. Serum samples were assayed for TSH ,FT4 and FT3 levels in Balsam Medical Lab.

3.9 Biochemical analysis

3.9.1 Determination of serum TSH

In the present study serum TSH was determined using a Microparticale Enzyme Immunoassay Technology. For this purpose Abbot full–automated Axsym immunoassay analyzer TSH assay system (Abbott laboratories, USA.) was used.

- **Principles**

AxSYM Ultrasensitive hTSH II is based on the Microparticle Enzyme Immunoassay (MEIA) technology. The AxSYM Ultrasensitive hTSH II reagents and sample are pipetted in the following sequence.

- **Sampling**
  - ❖ Sample and all AxSYM Ultrasensitive hTSH II reagents required for one test are pipetted by the Sampling Probe into various wells of a reaction vessel (RV).
  - ❖ Sample and Anti-hTSH Coated Microparticles are pipetted into one well of the RV forming an antibody-antigen complex. The RV is immediately transferred into the Processing Center. Further pipetting is done in the Processing Center with the Processing Probe.

- **Procedure**
  - ❖ An aliquot of the reaction mixture containing the antibody-antigen complex bound to the microparticles is transferred to the matrixcell. The microparticles bind irreversibly to the glass fiber matrix.
  - ❖ The matrix cell is washed with the LDS Wash Buffer.
  - ❖ The Anti-hTSH: Alkaline Phosphatase Conjugate is dispensed onto the matrix cell and binds with the antibody-antigen complex.
  - ❖ The matrix cell is washed to remove unbound materials.
  - ❖ The substrate, 4-Methylumbelliferyl Phosphate, is added to the matrix cell and the fluorescent product is measured by the MEIA optical assembly.

- **Reagents**
  - ❖ Bottle (14.1 mL) Anti-hTSH (Goat): Alkaline Phosphatase Conjugate in TRIS buffer with protein (bovine) stabilizers. Minimum concentration: 0.1 μg/mL. Preservative: Sodium Azide.
  - ❖ Bottle (9.0 mL) Anti-hTSH (Mouse, Monoclonal) Coated Microparticles in TRIS buffer with protein (bovine) stabilizers. Preservative: Sodium Azide.
  - ❖ Bottle (21.5 mL) LDS Wash Buffer containing surfactant.
  - ❖ Bottle (47 mL) TRIS Buffer. Preservatives: Sodium Azide and Antimicrobial Agents.
- **Expected values**

  The suggested normal range of the AxSYM Ultrasensitive hTSH II Assay is 0.5-5 μIU/mL.

3.9.2 Determination of serum FT4

AxSYM Free T4 is a Microparticle Enzyme Immunoassay (MEIA) for the quantitative determination of free thyroxine in human serum orplasma.

- **Principles**
  - ❖ AxSYM Free T4 is based on Microparticle Enzyme Immunoassay (MEIA) technology.
  - ❖ The AxSYM Free T4 Reagents and samples are pipetted in the following sequence
- **Sampling**
  - ❖ Sample and all AxSYM Free T4 reagents required for one test are pipetted by the Sampling Probe into various wells of a reaction vessel (RV).
  - ❖ The RV is immediately transferred into the Processing Center. Further pipetting is done in the Processing Center with the Processing Probe.
- **Procedure**
  - ❖ Sample and Anti-T4 Coated Microparticles are pipetted into one well of the RV forming an antibody-antigen complex.
  - ❖ An aliquot of the reaction mixture containing T4 bound to Anti-T4 Coated Microparticles is transferred to the matrix cell. The microparticles bind irreversibly to the glass fiber matrix.

❖ The matrix cell is washed with Solubilizer Solution to remove unbound materials.

❖ The T3: Alkaline Phosphatase Conjugate is dispensed onto the matrix cell and binds to the unoccupied antibody binding sites.

❖ The matrix cell is washed to remove unbound materials.

❖ The substrate, 4-Methylumbelliferyl Phosphate, is added to the matrix cell and the fluorescent product is measured by the MEIA optical assembly.

- **Reagents**

  ❖ AxSYM Free T4 Reagent Pack

  ❖ Bottle (15.2 mL) Solubilizer Solution. TRIS buffer containing surfactant. Preservative: Sodium Azide.

  ❖ Bottle (12.8 mL) T3: Alkaline Phosphatase Conjugate in TRIS buffer with protein stabilizers. Minimum concentration: 0.4 ng/mL. Preservative: Sodium Azide.

  ❖ Bottle (14.4 mL) Anti-T4 (Sheep) Coated Microparticles in TRIS buffer with protein stabilizers. Preservative: Sodium Azide.

  ❖ Bottle (50.2 mL) TRIS buffer. Preservatives: Sodium Azide and

  ❖ Antimicrobial Agents**.**

- **Expected values**

The suggested normal range for AxSYM Free T4 is 0.6-1.6 ng/dL.

3.9.3 Determination of serum FT3

AxSYM Free T3 is a Microparticle Enzyme Immunoassay (MEIA) for the quantitative determination of free triiodothyronine (free T3) in human serum or plasma on the AxSYM System**.**

- **Principles**

AxSYM Free T3 is based on the Microparticle Enzyme Immunoassay (MEIA) technology. The AxSYM Free T3 reagents and sample are pipetted in the following Sequence.

- **Sampling**
  - ❖ Sample and all AxSYM Free T3 reagents required for one test are pipetted by the Sampling Probe into various wells of a reaction vessel (RV).
  - ❖ The RV is immediately transferred into the Processing Center. Further pipetting is done in the Processing Center by the Processing Probe

- . **Procedure**
  - ❖ Sample and Anti-T3 Coated Microparticles are combined in one RV well.
  - ❖ The free (unbound) T3 in the sample binds to the Anti-T3 Coated Microparticles forming an antibody-antigen complex.
  - ❖ An aliquot of the reaction mixture, containing the antibody-antigen complex bound to the microparticles, is transferred to the matrix cell. The microparticles bind irreversibly to the glass fiber matrix.
  - ❖ The T3:Alkaline Phosphatase Conjugate is dispensed onto the matrix cell and binds to the available sites on the Anti-T3 Coated Microparticles.
  - ❖ The matrix cell is washed to remove unbound materials.
  - ❖ The substrate, 4-Methylumbelliferyl Phosphate, is added to the matrix cell and the fluorescent product is measured by the MEIA optical assembly.

- **Reagents**
  - ❖ AxSYM Free T3 Reagent Pack
  - ❖ Bottle (13.95 mL) LDS Wash Buffer containing surfactant.
  - ❖ Bottle (13.55 mL) T3 :Alkaline Phosphatase Conjugate in TRIS Buffer with protein (bovine) stabilizers. Minimum concentration: 0.4 ng/mL. Preservative: Sodium Azide.
  - ❖ Bottle (10.16 mL) Anti-T3 (Sheep, Monoclonal) Coated Microparticles in TRIS Buffer with protein (bovine and ovine) stabilizers. Preservative: Sodium Azide.
  - ❖ Bottle (50.20 mL) TRIS Buffer. Preservatives: Sodium Azide and Antimicrobial Agents.

- **Expected values**

The suggested normal range for AxSYM Free T3 1.8 to 4.7 pg/mL

3. 10 Statistical analysis

Data were computer analyzed using SPSS/PC (statistical package for the social science Inc., Chicago, Illinois USA, version 16.0).

- **Data analyses were carried out as follow**
  - ❖ Over viewing field questionnaire.
  - ❖ Coding of questionnaire.
  - ❖ Choosing data entry mode and data entry.
  - ❖ Data cleaning.
  - ❖ Defining and re-coding of certain variables.

Results were expressed as a mean ± SD. For comparison of the obtained variables between the study periods, we performed the Kruskal–Wallis rank test and x^2-test. Spearman's analysis was used to calculate the correlation coefficients. The Kologorov-Simirnove assess the normality of three variables among each group. one way ANOVA test is used. P value < 0.05 was marked as statistically significant.

RESULTS

CHAPTER 4
RESULTS

4.1 Characteristics of the study population

The present study is a cross sectional study, that included 170 women 90 pregnant and 85 non pregnant, from Gaza city. The mean age of pregnant was 24.9 years, and that of the non pregnant group was 29.3 years. The mean of gestational age of the cases was 8.7 weeks. The mean number of pregnancies for pregnant and non pregnant group was 3.5, 3.9 times, respectively and the mean number of abortions was 0.47 and 0.43 times, respectively (Table 4.1).

Table 4.1 General information of the pregnant and non pregnant groups.

Parameters	pregnant(n=90)		(n=80)non pregnant	
	Mean	S. D	Mean	S. D
Age (years)	24.9	5.6	29.3	5.4
Gestational age (weeks)	8.7	3.2	0.0	0.0
Number of pregnancies (times)	3.5	2.6	3.9	2.5
Number of abortions (times)	0.47	0.88	0.43	0.91

4.2 Serum TSH, FT4 and FT3 status in the study population

Table 4.2 indicated that 4 (2.4 %) of study population had elevated TSH levels (>5mIU/ml). 2 (2.2 %) in pregnant and 2 (2.5 %) in non pregnant so. Elevated FT4 level was found only in one pregnant (0.6%). Twelve subjects (7.1%) had elevated FT3 levels. 11 (12.9%) in pregnant and 1 (1.1%) in non pregnant.

Table 4.2 Thyroid stimulating hormone(TSH), FT4 and FT3 status in the study population.(n=170)

Elevated hormone	Subjects NO.(%)	pregnant NO.(%)	Non pregnant NO.(%)
TSH(mIU/ml)	4 (2.4)	2.0 (2.2)	2.0(2.5)
FT4(ng/d)	1 (0.6)	1 (0.6)	0.0
FT3 (pg/ml)	12 (7.1)	11(12.9)	1(0.6)

4.3 Serum thyroid hormone levels in pregnant and non- pregnant women

The mean of thyroid hormones in pregnant women in the first trimesters as well as, in non pregnant are shown in Table 4.3. There was no significant difference in the mean level of TSH between pregnant and non pregnant (mean =1.9 ±1.2 Vs1.9±0.94 mIU/ml, t=0.212, p=0.832). on other hand, the mean levels of FT4 and FT3 significantly increased in pregnant compared to non pregnant (mean = 0.96±0.30 and 3.1 ±1.4 Vs 0.88±0.19 ng/d and 2.7±0.69 pg/ml, p=0.041, 0.030, respectively).

Table 4:3 :Serum thyroid hormone levels in pregnant and non- pregnant women.

Parameters	pregnant (n=85)		non pregnant (n=85)		t	% Difference	p-value
	Mean	S. D	Mean	S. D			
TSH(mIU/ml)	1.9	1.2	1.9	0.94	0.212	0	0.832
FT4 (ng/d)	0.96	0.30	0.88	0.19	2.058	-9.1	0.041
FT3 (pg/ml)	3.1	1.4	2.7	0.69	2.199	14.8-	0.030

p> 0.05: not significant.
p<0.05: significant.

4.4 The Relation between thyroid hormones and pregnancy

The independent t-test showed that patients who suffer from thyroid problem had decreased mean levels of TSH compared to those who had not suffer ones(1.6± 0.36 Vs1.9±1.2 mIU/ml). These changes were not significant (t = 0.507, p =0. 6140) on other hand, the mean levels of FT4 and FT3 didn't also significantly between who suffer from thyroid problem and who had not (0.96 ±0.10 ng/d, 3.2±0.38 pg/ml Vs 0.96±0.31 ng/d, 3.1±1.4 pg/ml, p=0.730, p=0 .966, respectively).

Table :4.4 Results of thyroid   hormones in pregnant   women.

Are there problems in the thyroid gland		n	Mean	Std. Deviation	% Difference	t	p-value
TSH (mIU/ml)	Yes	3	1.6	0.36	-18.8	0.507	0.614
	No	87	1.9	1.2			
FT4 (ng/d)	Yes	3	0.96	0.10	0	0.346	0.730
	No	87	0.96	0.31			
FT3(pg/ml)	Yes	3	3.2	0.38	3.1	0.043	0.966
	No	87	3.1	1.4			

p> 0.05: not significant.
p<0.05: significant.

Table 4.5 demonstrates there was no significant difference in the mean level of TSH between who had not suffer from thyroid problem and who had suffer ones (1.9±0.87 Vs 3.1±2.02, p=0.912). Patients who had not suffer from thyroid problem had increased mean levels of FT4 compared to those who had suffer ones (0.86±0.19Vs 0.77±0.29 ng/d). However such changes were not significant (p=0.233). LikeFT3 were slightly decreased in Patients who had not suffer from thyroid problem compared to those who had suffer ones(2.7±0.66 Vs2.9±1.4pg/m), but these changes were not significant(p=0.566)

Table 4:5 Results of thyroid hormones in the non pregnant.

Are there problems in the thyroid gland		n	Mean	Std. Deviation	% Difference	p-value
TSH (mIU/ml)	No	77	1.9	0.87	38.7	0.912
	Yes	3	3.1	2.02		
FT4 (ng/d)	No	77	0.86	0.19	-11.7	0.233
	Yes	3	0.77	0.29		
FT3(pg/ml)	No	77	2.8	0.66	3.4	0.566
	Yes	3	2.9	1.4		

p> 0.05: not significant.
p<0.05: significant.

4.5 Assessment of thyroid hormones.

The mean levels of TSH, FT4 and FT3 for who had previous thyroid problem compared to those who had not are presented in Table 4.6. The mean level of TSH, FT4 and FT3 for those had previous thyroid problem(1.7±0.64mIU/m, 0.93±0.30ng/d , 3.1±0.95pg/m respectively) was found not significantly lower than that in those who had not are(1.9±1.2 mIU/ml, 0.96± 0.30 ng/d, 3.1±1.4pg/m) showing (p=0.755, 0.879, 0.901 respectively).

Table4:6 Assessment of thyroid hormones .in pregnant population who had previous thyroid problem.

Previous Thyroid problems		n	Mean	Std. Deviation	% Difference	t	p-value
TSH (mIU/ml)	Yes	3	1.7	0.64	-11.7	0.313	0.755
	No	87	1.9	1.2			
FT4(ng/d)	Yes	3	0.93	0.30	-3.2	0.152	0.879
	No	87	0.96	0.30			
FT3(pg/ml)	Yes	3	3.1	0.95	0	0.124	0.901
	No	87	3.1	1.4			

p> 0.05: not significant.
p<0.05: significant.

Table 4:7 illustrates the mean levels of TSH for who had not previous thyroid problem(1.94±0.88mIU/ml) was found not significantly lower than that compared to those who had ones in control population(2.6±1.75mIU/ml) showing p=0.630. On the other hand, no significant change was observed in the mean levels of FT4 and FT3 between who had not previous thyroid problem and those who had ones(0.89±0.19 Vs0.77±0.29 ng/d, 2.8±0.66, 2.8±1.2pg/m, p=0.208,p=0.477 respectively).

Table 4:7 Assessment of thyroid hormone .in non pregnant population who had previous thyroid problem.

Is there an analysis of the thyroid gland		n	Mean	Std. Deviation	% Difference	p-value
TSH (mIU/ml)	No	77	1.9	0.88	26.9	0.630
	Yes	4	2.6	1.8.		
FT4(ng/d)	No	77	0.89	0.19	-15.5	0.208
	Yes	4	0.77	0 .29		
FT3(pg/ml)	No	77	2.8	0.66	0	0.477
	Yes	4	2.8	1.2		

p> 0.05: not significant.
p<0.05: significant.

4.6 The Relation between family history of thyroid problems and results of pregnant women

As illustrated in Table 4.8 the mean levels of TSH, FT4 and FT3 showed increased in subject had history of thyroid problem in comparison to those who had not. These changes were not significant(t=0.678, p=0.499; t=1.516,p=0.133;t=.3790,p=0.705, respectively).

Table:4.8 pregnant whose family members were suffering from thyroid disease.

Is there one in the family suffers from problems in the thyroid gland		n	Mean	Std. Deviation	% Difference	t	p-value
TSH (mIU/ml)	yes	8	2.2	2.2	13.6	0.678	0.499
	No	82	1.9	1.1			
FT4(ng/d)	yes	8	1.1	0.22	14.5	1.516	0.133
	No	82	0.94	0.30			
FT3(pg/ml)	yes	8	3.3	1.2	6.1	0.379	0.705
	No	82	3.1	1.4			

p> 0.05: not significant.
p<0.05: significant.

Table:4.9 illustrates the mean level of TSH, FT4 and FT3 in non pregnant for those had history of thyroid problem(1.5±0.67 mIU/ml,0.75±0.05 ng/d,2.4±0.70 pg/ml, respectively) had decreased mean levels compared to those who had not(2.0±0.95 mIU/ml,0.89±0.19 ng/d, 2.8±0.68pg/m). These changes were not significant(p=0.073,p=0.087,p=0.600 respectively).

Table:4.9 non pregnant group whose family members were suffering from thyroid disease.

Is there one in the family suffers from problems in the thyroid gland		n	Mean	Std. Deviation	% Difference	p-value
TSH(mIU/ml)	Yes	6	1.5	0.67	-33.3	0.073
	No	74	2.0	0.95		
FT4(ng/d)	Yes	6	0.75	0.05	-18.6	0.087
	No	74	0.89	0.19		
FT3(pg/ml)	Yes	6	2.4	0.70	-16.6	0.600
	No	74	2.8	0.68		

p> 0.05: not significant.
p<0.05: significant.

4.7 The relation between genetic disease and thyroid hormone abnormalities

The relation between genetic diseases and the thyroid hormone status in pregnant is summarized in Table 4.10. The mean level of the TSH was(2.1±1.6 mIU/ml) for those who had genetic disease in their family showed increased in comparison to those who had not(1.9±0.12 mIU/ml). These changes were not significant (t=0.668, p=0.506). FT4 and FT3 showed non significant decreased between who had genetic disease in their family showed and those who had not(0.93±0.45 Vs0.97±0.26 ng/d, 2.8±1.6, 3.2±1.3 pg/ml, p=0.681, p=0.288, respectively)

Table4:10.the relation between genetic disease and thyroid hormone abnormalities. In pregnant group.

Are there genetic diseases in the family		n	Mean	Std. Deviation	% Difference	t	p-value
TSH (mIU/ml)	Yes	16	2.1	1.6	9.5	0.668	0.506
	No	74	1.9	0.12			
FT4(ng/d)	Yes	16	0.93	0.45	-4.3	0.413	0.681
	No	74	0.97	0.26			
FT3(pg/ml)	Yes	16	2.8	1.6	-14.2	1.070	0.288
	No	74	3.2	1.3			

p> 0.05: not significant.
p<0.05: significant.

The status of thyroid function in relation to genetic disease in non pregnant is illustrated in Table 4.11. There was no significant differences in the hormones levels of TSH,FT4 and FT3 between who had genetic disease in their family showed and those who had not (p=0.078, p=0.739, p=0.928, respectively)

Table 4:11. Genetic disease and thyroid hormone. In non pregnant group.

Are there genetic diseases in the family		n	Mean	Std. Deviation	% Difference	p-value
TSH (mIU/ml)	Yes	7	2.6	1.2	26.9	0.078
	No	73	1.9	0.89		
FT4(ng/d)	Yes	7	0.86	0.17	-2.3	0.739
	No	73	0.88	0.19		
FT3(pg/ml)	Yes	7	2.8	0.57	3.5	0.928
	No	73	2.7	0.70		

p> 0.05: not significant.
p<0.05: significant.

4.8 The Relation between thyroid problem and delivery.

Table 4.12 provides the relation between thyroid function and natural of delivery . The independent t-test showed that mean levels of TSH, FT4 and FT3 decreased slightly in patients who had normal delivery than patients who had abnormal delivery. .However, this difference was not significant(t=1.298, p=0.199; t=0.679,p=0.500; t=0.143,p=0.887, respectively).

Table 4:12 The Relation between thyroid problem and delivery. In pregnant group.

Was the previous, delivery normal		n	Mean	Std. Deviation	% Difference	t	p-value
TSH (mIU/ml)	abnormal delivery	9	2.41	1.9	-26.3	1.298	0.199
	Normal delivery	81	1.9	1.1			
FT4(ng/d)	abnormal delivery	9	1.1	0.38	-15.7	0.679	0.500
	Normal delivery	81	0.95	0.30			
FT3(pg/ml)	abnormal delivery	9	3.2	1.1	-3.2	0.143	0.887
	Normal delivery	81	3.1	1.4			

p> 0.05: not significant.
p<0.05: significant**.**

As indicated in Table 4.13. the mean level of TSH, FT4 and FT3 in patients who had abnormal delivery were higher than that patients who had normal delivery (2.3±1.2Vs1.9±0.89 mIU/m, 0.94±0.19 Vs 0.87±0.18 ng/d, 3.1±0.46 Vs2.7±0.72 pg/ml, respectively). This difference was not significant(p=0.402, p= 0.283, p=0.069 respectively).

Table 4:13 The Relation between thyroid problem and delivery in non pregnant group.

was the previous, delivery normal		n	Mean	Std. Deviation	% Difference	p-value
TSH (mIU/ml)	Abnormal-delivery	9	2.3	1.2	-21	0.402
	Normal delivery	71	1.9	0.89		
FT4(ng/d)	Abnormal-delivery	9	0.94	0.19	-8.1	0.283
	Normal delivery	71	0.87	0.18		
FT3(pg/ml)	Abnormal-delivery	9	3.1	0.46	-14.8	0.069
	Normal delivery	71	2.7	0.72		

p> 0.05: not significant.
p<0.05: significant.

4.9 The Relation between thyroid problem and hypertension in pregnancy.

The relation between hypertension and thyroid function in pregnancy is provided in Table 4.14. The independent t-test showed that patients with hypertension had decreased mean levels of TSH, FT4 and FT3 compared to those who had not(1.7±1.3 mIU/ml, 0.83±0.44ng/d, 2.5±1.49pg/m Vs1.9±1.2 mIU/ml, 0.97±0.29 ng/d, 3.2±1.4 pg/ml respectively). These changes were not significant(t=0.380, p=0.705; t=1.063,p=0.291; t=1.241, p=0.218, respectively).

Table 4:14 **The Relation between thyroid problem and hypertension during**

pregnancy.

Hypertension during Pregnancy		n	Mean	Std. Deviation	% Difference	t	p-value
TSH (mIU/ml)	Yes	6	1.7	1.3	-11.7	0.380	0.705
	No	84	1.9	1.2			
FT4(ng/d)	Yes	6	0.83	0.44	-16.8	1.063	0.291
	No	84	0.97	0.29			
FT3(pg/ml)	Yes	6	2.5	1.5	8	1.241	0.218
	No	84	2.3	1.4			

p> 0.05: not significant.
p<0.05: significant.

Hypertension in relation to thyroid hormones levels in non pregnant is shown in Table 4.15. The mean of TSH, FT4 and FT3 levels showed a slightly difference in patients who had hypertension in comparison to those who had not. These changes were not significant(p=0.972, p=0.674, p=0.108, respectively)

Table **4.15The Relation between thyroid problem and hypertension in non**

pregnant group.

Hypertension Pregnancy		n	Mean	Std. Deviation	% Difference	p-value
TSH mIU/ml)	Yes	5	1.9	0.76	0	0.927
	No	75	1.9	0.96		
FT4(ng/d)	Yes	5	0.84	0.17	-4.7	0.67
	No	75	0.88	0.19		
FT3(pg/ml)	Yes	5	2.7	0.96	-3.7	0.108
	No	75	2.8	0.67		

p> 0.05: not significant.
p<0.05: significant.

4.10 The relation between thyroid hormone and age.

   In order to test the equality of means between the three age groups with respect to the three variables, we need to assess the normality of three variables among each group. The Kologorov-Simirnove test shows that most of them are not normally distributed except the FT3 at age group (18-25) and TSH for age group (34-40) as

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shown in Table 4.16 Thus the parametric test the One way ANOVA can't be used, Alternatively, we can use Kruskal Wallis test as a non parametric test.

Table **4.16 The Kologorov-Simirnove test for age group.**

Age1		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
18-25	TSH (mIU/ml)	0.183	45	0.001	0.916	45	0.003
	FT4(ng/d)	0.161	45	0.005	0.922	45	0.005
	FT3(pg/ml)	0.085	45	0.200	0.956	45	0.086
26-33	TSH mIU/ml)	0.166	61	0.000	0.901	61	0.000
	FT4 (ng/d)	0.165	61	0.000	0.910	61	0.000
	FT3(pg/ml)	0.121	61	0.027	0.953	61	0.021
34-40	TSH mIU/ml)	0.161	22	0.142	0.908	22	0.043
	FT4 (ng/d)	0.194	22	0.031	0.900	22	0.029
	FT3(pg/ml)	0.194	22	0.030	0.900	22	0.030

Kruskal Wallis tests shows that there is no significant difference between the means of the three Variables with respect to the age groups were the p-values is greater than 0.05 as shown in Table 4.17.

Table **4.17 The relation between age and the thyroid hormone in pregnant**

	TSH mIU/ml)	**FT4**(ng/d)	**FT3**(pg/ml)
Chi-Square	0.658	1.827	1.201
p-value	0.720	0.401	0.549

In non pregnant population where the mean of the age was 25.3 year when divided into group, *Kruskal Wallis Test is used.* There is a significant statistical difference between the groups of age for FT4 and FT3 As the p- value was 0.034 and 0.038. as shown in Table 4.18.

Table **4.18 The relation between age and the thyroid hormone in non pregnant group.**

	TSH mIU/ml)	FT4(ng/d)	FT3(pg/ml)
Chi-Square	0.171	6.779	6.541
p- value .	0.918	0.034	0.038

4.11 The relation between thyroid function and gestational age

As depicted from Table 4.19, there was no significant association between increasing in gestational age and TSH, FT4 and FT3(p=0.09, 0.575,0.685, respectively)

Table **4.19 The relation between thyroid function and gestational age**

		n	Mean	Std. Deviation	**% Difference**	t	p-value
TSH (mIU/ml)	9-13w	54	1.8	0.96	18.1	1.712	0.09
	1-8 w	36	2.2	1.5			
FT4(ng/d)	9-13w	54	0.97	0.27	-4.3	0.562	0.575
	1-8 w	36	0.93	0.35			
FT3(pg/ml)	9-13w	54	3.2	1.3	-3.2	0.407	0.685
	1-8 w	36	3.1	1.5			

W :(gestational age in weeks)

p> 0.05: not significant.
p<0.05: significant.

4.12 The relation between the thyroid function and the number of pregnancies.

For the control population the mean of number of pregnancies was 3.9 times .there is no correlation between the number of pregnancies and the TSH, FT4 and FT3(p=0.537, p=0.864, p=0.391) as shown in Table 4.20

Table **4.20 The relation between the thyroid function and the number of pregnancies.**

		TSH (mIU/ml)	FT4 (ng/d)	FT3(pg/ml)
Number of pregnancies	Pearson Correlation	-0.071-	0.020	0.100
	Sig. (2-tailed)	0.537	0.864	0.391

While the mean of number of pregnancy was 3.4 times case population. there is no correlation between the number of pregnancies and the TSH, FT4 and FT3(p=0.423,p=0.220,p=0.867) as shown in Table 4.21 .

Table **4.21 Number of pregnancies and thyroid hormone in cases.**

		TSH (mIU/ml)	FT4(ng/d)	FT3(pg/ml)
Number of pregnancies	Pearson Correlation	0.088	0.136	0.022
	Sig. (2-tailed)	0.423	0.220	0.867

DISCUSSION

CHAPTER (5)
DISCUSSION

Specific reference intervals for FT4, T4, T3 in addition to TSH during pregnancy may be particularly important for several reasons. First, it would be important to know what the FT4 levels are in the first trimester as they are higher than in other trimesters in a euthyroid pregnancy, and this is time when the fetus is wholly dependent on T4 from the mother. Accurate reference intervals for T4 and FT4 would then provide the ability to detect a deficiency at this critical time and provide a subtle indication of maternal hypothyroidism. Such hypothyroxinemia may be masked during the first trimester if that determination relied solely on an elevated TSH because of the stimulatory effect of high hCG levels on the thyroid gland. It is possible that high, sustained estrogen levels during this time are associated with transient lowering of serum TSH (120,121). Thus curtailing its rising above the normal non pregnant range. Second maintenance of normal maternal thyroid hormone levels is known to be a determinant of adequate fetal thyroid hormone levels early in pregnancy (122 and adequate mental and psychomotor development in infants (123) Better and easier measurements of T4 and FT4 during early pregnancy would contribute to better insights into the more appropriate method of detecting thyroid deficiency at this critical time for the fetus. Mild maternal hypothyroidism (subclinical hypothyroidism) has been implicated as the cause of neuro-psycho-intellectual deficit in offspring (78,124). Accurate reference intervals in early pregnancy would make it possible to better define this condition. In cases of overt hypothyroidism the fetal consequences can be extreme (125). However, it appears that the maternal level and delivery of FT4 and not T3 to the fetus is critical for the neuropsychological development of the fetus (80). A deficiency may not be reflected by the degree of TSH elevation (126). It is imperative for normal intervals of thyroid hormones to be established for pregnant women especially it should be determined in early pregnancy and particularly T4 level which can be used to screen the fetus and pregnancy risk.

This is the first study to investigate the status of thyroid function and to evaluate the effects of age, number of pregnancies, gestational age, family history of

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thyroid problems, and genetic diseases on thyroid function. This could be useful in adopting strategies which may be applied for pregnant women.

5.1 General characteristics of the study population

Data presented in this study dealt with 170 women's 80 non pregnant (controls) and 90 pregnant women's. The mean age of the cases in the present study was 24.8±5.6 years. This mean age was in the range to that reported in study measured blood levels of (TSH), (FT4) and (FT3) for normal pregnant women randomly selected with mean age of (28 ± 12) years(116).

5.2 Hypothyroidism and Hyperthyroidism in pregnant women.

Hypothyroidism was observed in 2.2% of our population which is similar to that in European and American pregnant women where the prevalence was 2.2% and 2.5% respectively. (127-131). Our results are lower than those reported for pregnant women in Tunisia which was 3.2%. However, iodine deficiency could contribute to the development of hypothyroidism in some of these women in our study. While the Gaza city is considered as marginally iodine sufficient, the increase of iodine requirement during pregnancy may cause substantial iodine deficit that induces thyroid insufficiency, which may be due to the use of non-iodized salt in Gaza city. The higher prevalence of hypothyroidism in advanced gestation suggests that iodine deficiency is probably a key contributor of hypothyroidism in our pregnant women. Hypothyroidism might be caused by defect in iodine metabolism. However, following iodine metabolism in the study group was beyond the objectives of this research. Also the economic situation in the country does not allow the presence of system with prefect food for pregnant women. This system should provide protection to pregnant women of any malnutrition during pregnancy. Other reasons for higher prevalence of hypothyroidism in our study may be due to the remnants of war (like as perchlorate contaminates, Perchlorate acts by inhibiting the thyroid's ability to take up the nutrient iodide, which is a key building block for thyroid hormones. If the thyroid gland does not have enough iodide for a sufficient period of time, the body's thyroid hormone levels will eventually drop.) in the recent contamination of water and soil which may have negative impact on the thyroid function .

Another cause might be due to misuse of Pesticides by farmers, this lead to contamination of vegetables and fruits which ultimately affects human health(132).

Hyperthyroidism was observed in 1.0 % of our pregnant women , it was more or less similar than that reported in Tunisia (1.3%). Because diagnosis was based solely on TSH value, the etiology of hyperthyroidism was uncertain. Another cause of hyperthyroidism may be due to ignorance of women who do not seek medical advise.

5.3 Thyroid parameters in pregnant and non pregnant women.

This study showed a significant difference between pregnant and non-pregnant women. in relation to FT4 and FT3 means. However, The mean TSH level of pregnant women was lower than that of non-pregnant women, but did not show a significant difference between pregnant and non-pregnant women. Similar studied have revealed the mean TSH level in the study was closely similar to what we found (116,133).

Panesar and his colleagues found that the FT3 decreased during pregnancy, while the FT4 initially increased, peaking between 9-13 weeks(134) In our study, changes in the serum levels of FT4 in pregnant women were closely similar to the previous study. We also found that the highest level of FT3 was during the first trimester, Similar to that found in the study in china (116). It seems that the target groups of different researches share many characteristics like living conditions and social habits.

On the other hand, the present results were not concordant with some other studies in this field. Kurioka and his colleagues reported significantly reduced levels of free T3 and free T4(135). Also, Kumar reported that TSH values were increased steadily with each trimester(110).

Our results are similar to those reported by Marwaha with the exception of the free T4 values(136). However, the difference between our study and theirs may be due to the fact that our samples were collected during the first-trimester of pregnancy.

5.4 The Relation between thyroid hormones and pregnancy

Data revealed that there is no significant difference between those who had abnormal thyroid hormones and those who had normal hormones levels in cases group as in control group. the group who had abnormal thyroid function had elevated TSH but normal FT4This means that they had subclinical hypothyroidism (59). also known as mild hypothyroidism that has not progressed.(137)

5.5The Relation between family history of thyroid problems and results of pregnant women and non pregnant women.

Data revealed that there is no significant difference in subjects who had history of thyroid problem in their family and subjects who did not have family thyroid problem. In our society the habits does not allow the person to declare about disease in his family, even those who declares of having family history of thyroid problems may not be first –class kinship to pregnant women. The number of cases who had family history of thyroid problems are small compared to the total sample size. Vaidya have reported that targeted thyroid function testing of only pregnant women at high risk for thyroid disease (e.g. family history of thyroid disease) would miss about one-third of women with overt and subclinical thyroid disease(138).

5.6 The relation between genetic disease and thyroid hormone abnormalities

Data revealed that there is no significant difference in subjects who had genetic diseases and those who do not have. This applies to both case and control groups. It seems that women are not educated enough to understand the nature of genetic disease

5.7 The Relation between thyroid problem and hypertension in pregnancy.

Our results do not show any relationship between thyroid function and hypertension, this may be due to adequate follow up of each subject was not done. During early pregnancy, blood pressure levels normally decrease, but during the second and third trimesters, they begin to steadily rise. If blood pressure was high in pregnancy, known as *chronic hypertension*; if first develop hypertension only after the first twenty weeks of pregnancy, *its gestational hypertension.* develop gestational hypertension if,

- Hypothyroid

• Experiencing a first pregnancy

• Have a kidney disease

• Have diabetes (chronic or gestational)

• Are not eating well

Women with chronic hypertension tend to have a family history of hypertension. Chronic hypertension is more common in women over thirty-five and is aggravated by smoking, obesity, or kidney problems.(24)

5.8 The relation between thyroid hormone and age.

Results of the control group showed significant relationship between age and both FT3 and FT4.

This may be due to fact that the mean age of the control(29.32 years) which is more than the mean age of cases(24.89 years). this is in agreement with other studies, in multivariate models, TSH increased by 0.03 mIU/L for every additional year of maternal age ($P = .03$) (139**).** Also reported that TSH showed significant differences ($P < .005$) according to the age of the mother(140).

5.9 The relation between thyroid function and gestational age.

TSH level during the first few weeks was higher than the subsequent weeks. It seems that TSH levels are affected by the level of HCG. High level of HCG are accompanied by lower levels of TSH and vice versa(4,99). However, we did not assess the levels of HCG because this was not planned during the preparation of our proposal.

CONCLUSSIONS

&

RECOMMENDATIONS

Chapter (6)

CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

1. Hypothyroidism was observed in 2.38 % of our population, 2.2% in pregnant women and (2.5%) in non pregnant women. While hyperthyroidism was observed in 1.0 % of our pregnant women.

2. The study showed a significant difference between pregnant and non-pregnant women in relation to FT4 and FT3 level.

3. The mean TSH levels of pregnant women was lower than the mean level of non pregnant. However these results were not statistically significant**.**

4. There was no significant difference between those who had abnormal thyroid hormones and those who had normal hormones levels in cases as well as in control group.

5. There was no significant difference between those who had history of thyroid problem in their family and those who did not have history of thyroid problem in their family in cases as well as in control group.

6. There was no significant difference between those who had genetic disease in their family and those who did not in both cases and in control.

7. There is no significant difference between those who had past abnormal delivery and those who had past normal delivery.

8. There was no significant difference between those who had hypertension during pregnancy and those who did not have hypertension .

9. There was significant relationship between age and both FT3 and FT4 in the control group.

10. . There was no significant difference between thyroid function and gestational age.

6.2 Recommendations

1- Thyroid function testing TSH and FT4 studies prior to conception or in early pregnancy is recommended.

2 -Pregnant women in the following categories should have thyroid function assessed either at diagnosis or at antenatal booking, or even before conception if feasible type-1 diabetes, previous history of thyroid disease, current thyroid disease, family history of thyroid disease, goiter, symptoms of hypothyroidism

3- Assessment thyroid peroxidase (TPO) antibodies**.**

4- Assessment of HCG level in the first trimester of pregnancy.

5-More research concerning thyroid gland should be performed to include 2nd and 3rd trimester with larger sample size.

 6-It is recommended to launch a program aiming at determination of normal levels of thyroid hormones during the three phases of pregnancy.

7- The relationship between thyroid hormones and other hormones during pregnancy should be investigated.

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(Annex 1)

Palestinian National Authority
Ministry of Health
Helsinki Committee

السلطة الوطنية الفلسطينية
وزارة الصحة
لجنة هلسنكي

التاريخ: 2010/3/23

Name:
I would like to inform you that the committee has
discussed your application about:

الاسم :رغدة راضي
نفيدكم علماً بأن اللجنة قد ناقشت مقترح دراستكم
حول:-

Assessment of thyroid function in pregnant
women from Rimal Health Center Gaza City.

In its meeting on March   2010

و ذلك في جلستها المنعقدة لشهر 3   2010

and decided the Following:-

و قد قررت ما يلي:-

To approve the above mention research study.

الموافقة على البحث المذكور عاليه.

Signature
توقيع

Member   Member   Chairperson

عضو   عضو

Conditions:-
❖ Valid for 2 years from the date of approval to start.
❖ It is necessary to notify the committee in any change in the admitted study protocol.
❖ The committee appreciate receiving one copy of your final research when it is completed.

The Palestinian National Authority

Ministry of Health

Directorate General of Human Resources Development

السـلطة الوطنية الفلسطينيـة

وزارة الصحـة

الإدارة العامـة لتنمية القوى البشريـة

(Annex2)

الرقم: ٩٢٦.... / ١٥

التاريخ: 2010/04/08

الأخ الدكتور/ فؤاد العيسوي   المحترم،،،

مدير عام الرعاية الأولية

تحية طيبة وبعد،،،

<u>الموضوع/ تسهيل مهمة باحث</u>

بخصوص الموضوع أعلاه، يرجى تسهيل مهمة الباحثة/ رغدة عبد اللطيف راضي الملتحقة ببرنامج ماجستير العلوم الحياتية – تخصص تحاليل طبية – للجامعة الإسلامية حيث تقوم بإجراء البحث النهائي بعنوان:-

" تقييم وظائف الغدة الدرقية في النساء الحوامل"

حيث ستقوم الباحثة بتعبئة الاستبانة من النساء الحوامل المراجعات لعيادة صحة الأم والطفل (عيادة الرمال) وأخذ جزء من عينات الدم التي تسحب من الأمهات لإجراء فحوصات لتقييم وظائف الغدة الدرقية، وذلك بما لا يتعارض مع مصلحة العمل وضمن ضوابط وأخلاقيات البحث الصحي دون تحمل الوزارة أي أعباء مع أخذ موافقـة الأمهـات الخطية قبل إجراء البحث.

وتفضلوا بقبول خالص الاحترام والتقدير،،،،،،

د. ناصر رأفت أبو شعبان

مدير عام تنمية القوى البشرية

(Annex3)

الأخوات العزيزات السلام عليكم ورحمة الله و بركاته

يهدف البحث إلى معرفة تأثير الحمل على وظائف الغده الدرقيه في مدينه غزه ، وعليه يتطلب
البحث الاجابة على بعض الأسئلة القصيرة الموضحة في الاستبانة التالية ، و أخذ عينة دم
بسيطة.

			1. تاريخ سحب العينة
			2. العمر
			3. اسبوع في الحمل
			4. عدد مرات الحمل
لا ( )		نعم ( )	5. هل سبق أن عائلتي من مشاكل في الغده الدرقيه
لا ( )		نعم ( )	6. هل يوجد احد في العائله يعاني من مشاكل الغده الدرقيه
لا ( )		نعم ( )	7. هل سبق أن قمتي بعمل تحاليل للغده الدرقيه اثناء الحمل
			8. هل كانت الولادات السابقه طبيعيه
			9. هل كانت هناك امراض وراثيه في الولادات السابقه
			10. هل تعاني من مرض السكر اثناء الحمل او قبل الحمل
			11. هل يرتفع ضغط الدم اثناء الحمل

نتائـــج تحليـل عينة الدم

TSH	
FT4	
FT3	