"A CASE CONTROL STUDY TO EVALUATE THE CORRELATION OF HYPOTHYROIDISM IN PREGNANT WOMEN WITH ADVERSE PREGNANCY OUTCOME COMPARED TO PREGNANT WOMEN WITH NORMAL PREGNANCY OUTCOME"

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ENDORSEMENT

This is to certify that the dissertation entitled **"A CASE CONTROL STUDY TO EVALUATE THE CORRELATION OF HYPOTHYROIDISM IN PREGNANT WOMEN WITH ADVERSE PREGNANCY OUTCOME COMPARED TO PREGNANT WOMEN WITH NORMAL PREGNANCY OUTCOME"** is a bonafide research work done by **(REG.NO. BJ0111004).**

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LIST OF ABBREVIATIONS USED

AB	-	Abortion
AP	-	Abruptio Placenta
ATD	-	Anti thyroid drugs
ANC	-	Antenatal care
BMR	-	Basal metabolic rate
CI	-	Confidence interval
CS	-	Caesarean section
DI	-	De-Iodinase
DIT	-	Di-Iodothyronine
FT3	-	Free triiodothyronine
FT4	-	Free Thyroxine
GDM	-	Gestational Diabetes Mellitus
GIT	-	Gastrointestinal tract
GTD	-	Gestational trophoblastic disease
HCG	-	Human Chorionic Gonadotropin
IUGR	-	Intra Uterine Growth restriction
IRR	-	Pregnancy specific Indian Reference Ranges
LMP	-	Last menstrual period
LT4	-	Levothyroxine
LBW	-	Low Birth weight
MIT	-	MonoIodothyrosine
OD	-	Odd's ratio
OH	-	Overt Hypothyroidism
PE	-	Pre eclampsia

PTD	-	Pre Term delivery
PPT	-	Post partum Thyroiditis
rT3	-	Reverse riiodothyroidism
SCH	-	Sub Clinical Hypothyoroidism
RR	-	Risk ratio
SB	-	Still birth
Tab	-	Thyroid auto antibodies
TES	-	Thyroid endocrine society
TPOAB	-	Thyroid peroxidase antibodies
TgAB	-	Thyroglobulin antibodies
TRAB	-	Thyroid receptor antibodies
TSI	-	Thyroid stimulating immunoglobulins
TD	-	Thyroid disorder
Tg	-	Thyroglibulin
TPO	-	Thyroid peroxidase
TSH-R	-	Thyroid stimulating hormone receptor
TSH	-	Thyroid stimulating hormone
T4	-	Thyroxine
T3	-	Triidothyronine
T2	-	Diidothyronine
TBG	-	Thyroid binding globulin
TBPA	-	Thyroxine binding pre albumin
TRH	-	Thyroid releasing hormone
T-CELL	-	Treg cells

ABSTRACT

Background: Thyroid dysfunction is one of the most common endocrine disorders affecting women of reproductive age group including pregnancy. In pregnancy overt hypothyroidism is seen in 0.2%[1] cases and sub-clinical hypothyroidism in 2.3%[2] cases. On the whole the reported prevalence of thyroid disorders during pregnancy ranges from 2 to 5% in pregnant women[3&4].This is because pregnancy increases the demand on maternal thyroid gland. When mother fails to cope with this she develops hypothyroidism. Untreated or uncontrolled hypothyroidism is associated with Abortions, Pregnancy Induced Hypertension, Placental Abruption, Preterm labour, IUGR, Gestational diabetes, IUD , lead to increased cesarean deliveries, NICU admissions and reduced intellectual function in the offspring.[6] Treated hypothyroidism was not associated with any increase in maternal, fetal or neonatal complications and did not affect the mode of delivery.[7]

Objective: To evaluate the association of hypothyroidism in pregnant women with adverse pregnancy outcome and compare it with pregnant women with normal pregnancy outcome and to compare the association of Hypothyroidism using trimester specific Thyroid Endocrine Society (TES)criteria and trimester specific Indian reference range (IRR)criteria pregnancy specific cut off values for the diagnosis of hypothyroidism.

Methodology:

Design: one year Case control study.

Setting: KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, KLE University's teaching hospital attached to Jawaharlal Nehru Medical College Belgaum

Study Period: One year from January 2012 to December 2012.Sample Size: 200cases and 200 controls

Inclusion criteria:

Cases: Pregnant women with minimum of any one of the following pregnancy complications in the present pregnancy Abortions, Hyperemesis gravidarum, Preterm delivery , IUGR , Preeclampsia/Gestational hypertension, IUD, Gestational diabetes, Abruptio placenta, And

*Controls***:** Pregnant women at similar gestational age with no previous or present pregnancy complication were recruited as controls.(Where ever applicable)

Exclusion criteria : Is Pregnant women with previously diagnosed thyroid dysfunction/ autoimmune disorder, family history of thyroid dysfunction, Multiple pregnancy& hyperthyroidism Patient related information was collected and entered in to data collection instrument (Annexure II) after taking Informed written consent from the women from both cases and controls and they were subjected to testing of Sr.TSH, Free T3 and Free T4 levels only once. 2ml of blood samples was collected in a plain vaccutainer and sent to laboratory. At the laboratory FT3, FT4 & TSH levels are assessed and then analyzed by

1. Trimester specific cutoffs recommended by Thyroid Endocrine Society(TES)

2. Trimester specific cutoffs recommended for Indian pregnant women by RK Marwaha and et al that is the Indian reference range(IRR)criteria.

Results: In the present study it was observed that the prevalence of hypothyroidism is significantly higher in cases when compared to controls according to trimester specific

TES criteria (p=0.001) and IRR criteria (p=0.0001) values as cutoffs and the Odd's ratio of 11.27 and 95% confidence interval between cases and controls (6.3 & 20.15).

When individual complications of pregnancy and association with hypothyroidism were considered it was observed that 48.5%(TES) of Preeclampsia cases were found to be hypothyroid and with the highest odds ratio of 10.7(95% confidence interval between 5.58-20.7) Increased association was observed for Abruption(OD-8.6 95% CI-3.48-21.34), spontaneous abortions(OD-7.5 95%CI-3.28-17.5), Intra uterine growth retardation(OD-7.4 95%CI-3.72-15.05) gestational diabetes mellitus(OD-6.9 95%CI-2.86-16.6), and Intra uterine death(OD-6.0 95%CI-2.3-15.8) and the least association was observed with spontaneous preterm births (OD-1.9 95%CI-0.5-7.2)

Conclusion:

More number of hypothyroid women can be detected by using the trimester specific thyroid endocrine society cutoff values than to trimester specific Indian reference range cutoff values for pregnancy as the cutoff value of S.TSH is lower for TES criteria. So for a clinical set up it is recommended to follow TES criteria for the screening of hypothyroidism in pregnancy.

Hence Until the controversy regarding Universal screening versus screening for targeted high risk pregnant women settles, it is advisable to offer screening for women with present adverse pregnancy outcome. It is worthwhile screening these women as hypothyroidism can be detected especially Subclinical hypothyroidism early and treated by LT4 replacement would probably reduce adverse pregnancy outcomes associated with hypothyroidism.

Key words: Hypothyroidism; Low risk pregnancy; Adverse pregnancy .TSH screening, Free T4, Free T3.

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INTRODUCTION

Thyroid dysfunction is one of the most common endocrine disorders affecting women of reproductive age group including pregnancy. In pregnancy overt hypothyroidism is seen in 0.2%[1] cases and sub-clinical hypothyroidism in 2.3%[2] cases. On the whole the reported prevalence of thyroid disorders during pregnancy ranges from 2 to 5% in pregnant women[3&4].This is because pregnancy increases the demand on maternal thyroid gland. When mother fails to cope with this she develops hypothyroidism. Overt hypothyroidism causes infertility and amenorrhea. While it is the borderline or the Subclinical hypothyroids and inadequately treated hypothyroids who present with problems in pregnancy.

Untreated or uncontrolled hypothyroidism is associated with Abortions, Pregnancy Induced Hypertension, Placental Abruption, Preterm labour, IUGR, Gestational diabetes, IUD , lead to increased cesarean deliveries, NICU admissions and reduced intellectual function in the offspring.[6] Treated hypothyroidism was not associated with any increase in maternal, fetal or neonatal complications and did not affect the mode of delivery.[7]

Diagnosis of thyroid disorder based on the symptoms of hypo/ hyperthyroidism are often missed because of the non specific symptoms and hyper metabolic state of pregnancy and another reason to miss out the diagnosis is because during the early weeks of pregnancy, a fall in serum TSH and increase in free thyroxine (FT4) level is observed that may mask the diagnosis of hypothyroidism. The reference range for normal serum TSH level in non pregnant women is 0.45–4.5mU/L, with more than 95% of individuals having a value below 2.5 mU/L. Hence

Gestation age specific TSH thresholds from large population based studies seem to be the best way to increase diagnostic accuracy of hypothyroidism in pregnancy.

In view of potential for serious adverse pregnancy outcome associated with maternal thyroid disease and the proved benefits of treatment many organizations have recommended routine thyroid function screening in pregnancy. But as such routine screening and treatment of subclinical hypothyroidism during pregnancy is not yet strictly recommended and is still a debated issue.

NEED FOR THE STUDY

Most of the studies done on hypothyroidism in pregnancy have concluded that high risk cases such as with family history, previously diagnosed thyroid disorders and autoimmune diseases have higher incidence of adverse maternal and fetal outcome. But cases with previous or present adverse pregnancy outcome without past or family history of thyroid disorders have not been included in the high risk group for thyroid screening in pregnancy.

There are isolated studies which have reported the correlation of hypothyroidism and specific pregnancy adverse complications such as association between hypothyroidism with preeclampsia and hypothyroidism with IUGR, but to our best of knowledge, there has been no case control study to assess the association of hypothyroidism considering the present adverse pregnancy complication as a criteria for thyroid screening during pregnancy.

Policy considerations concerning routine thyroid screening before or during pregnancy remain controversial and a subject of debate. As for instance, the results of screening might induce unnecessary anxiety, optimal timing of screening has not been determined and if universal screening is to become mandatory then any deviation from the accepted guidelines might be a cause of legal suits. Between 2000 & 2004, The American College of Obstetricians and Gynecologists (ACOG), American Thyroid association (ATA) and a consensus panel involving American Association of Clinical Endocrinologists (AACE) and the Endocrine Society (ES) have found insufficient evidence to recommend routine thyroid screening in pregnancy and have not endorsed it.

In 2005, an International Advisory committee was established under the auspices of the American Endocrine Society to review the best evidence for thyroid disorders associated with pregnancy and to develop evidence based guidelines for clinical practice. However after reviewing the available evidence the committee was of the opinion that there is lack of randomized controlled studies evaluating the impact of medical intervention on the adverse outcomes associated with thyroid abnormalities during pregnancy and post partum and hence precluded a recommendation for universal screening. Controlled Antenatal Thyroid Screening (CATS) is a prospective randomized Controlled study currently in progress and led by Dr. John Lazarus, in Wales This study is designed to directly test the value of screening for thyroid disease during pregnancy and treating all the women with elevated serum TSH level. The results of this study might settle out the controversies regarding universal screening during pregnancy.[10]

In a country like India with resource limited settings, universal thyroid screening had not been adopted as a standard care for antenatal women but has been confined to only cases with known thyroid disorder and with recurrent pregnancy loss. There are very few studies done on hypothyroidism during pregnancy on Indian women.

Hence our case control study is aimed to evaluate the association of hypothyroidism in pregnant women with adverse pregnancy outcome and compare it with pregnant women with normal pregnancy outcome.

OBJECTIVES

The objective of the present study is:

-To evaluate the association of hypothyroidism in pregnant women with adverse pregnancy outcome and compare it with pregnant women with normal pregnancy outcome.

-Compare the association of Hypothyroidism using Thyroid Endocrine Society (TES) and Indian reference range (IRR) pregnancy specific cut off values.

REVIEW OF LITERATURE

The thyroid gland is a butterfly shaped endocrine gland first described by Sir Thomas Wharton (1616-1673) of England. The word thyroid is derived from Greek words ("*thyreos*"-shied, plus "*eidos*"-form). It weighs normally between 12-20grams. It has 2 lobes which are connected by an isthmus. It's highly vascular. The right lobe is normally more vascular than the left and it is often the larger of the two and tends to enlarge more in disorders associated with a diffuse increase in gland size. Two pairs of vessels constitute the major arterial blood supply, the superior thyroid artery which arises from the external carotid artery and the inferior thyroid artery which arises from the subclavian artery. It receives both sympathetic and parasympathetic nerve supply. Sympathetic nerves control the blood supply of the thyroid gland. An estimate of thyroid blood flow range from 4 to 6 mL/minute per gram, Enlargement of the thyroid gland is called Goiter. In diffuse toxic goiter resulting from Grave's disease, blood flow may exceed 1 L/minute and may be associated with an audible bruit or even a palpable thrill and secretes excess thyroid hormones. Non toxic goiter secretes normal or even subnormal levels of hormones.[11&12.]

The thyroid gland develops from the floor of the primitive pharynx during the third week of gestation. The developing gland migrates along the thyroglossal duct from the foramen cecum at the base of the tongue to reach its final location in the neck. This feature accounts for the rare ectopic location of thyroid tissue at the base of the tongue (lingual thyroid) as well as the occurrence of thyroglossal duct cysts along this developmental tract. Fetal thyroid hormone synthesis normally begins at about 11 weeks' gestation.[11]

Thyroid gland development is controlled by the coordinated expression of several developmental transcription factors. Thyroid transcription factor (TTF)-1, TTF-2 and paired homeobox-8 (PAX-8) are expressed selectively, but not exclusively, in the thyroid gland. In combination they dictate thyroid cell development and the induction of thyroid-specific genes such as thyroglobulin (Tg), thyroid peroxidase (TPO), the sodium iodide symporter (Na^+/I, NIS), and the thyroid-stimulating hormone receptor (TSH-R). Mutations in these developmental transcription factors or their downstream target genes are rare causes of thyroid agenesis or dyshormonogenesis and congenital hypothyroidism.[11]

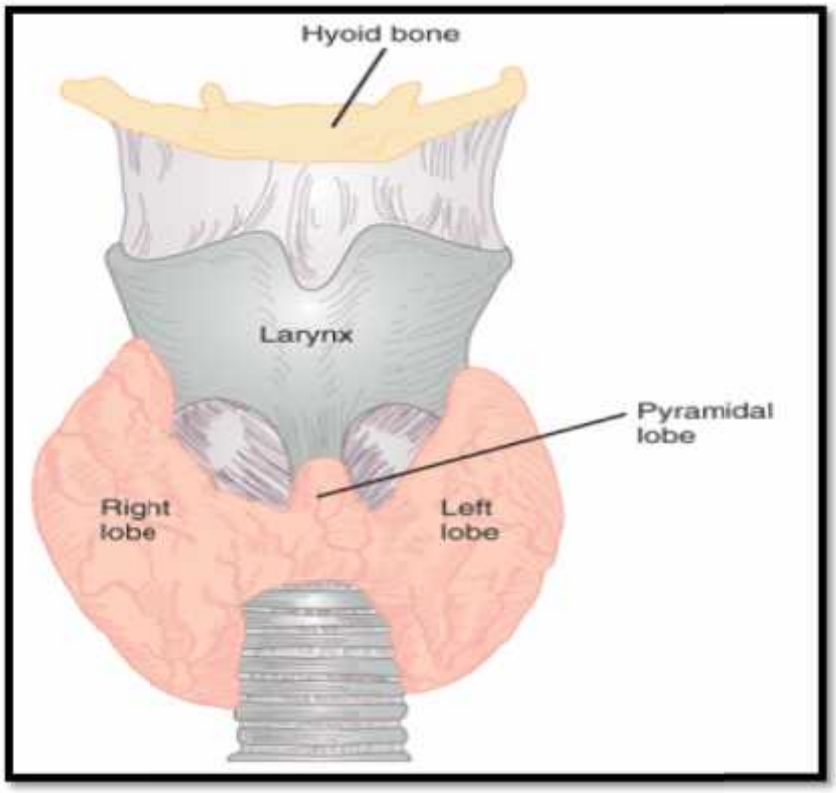


Fig1:Thyroid gland

MICROSCOPIC FEATURES:

The gland is composed of closely packed, spherical units termed *follicles,* which have a rich capillary network. The interior of the follicle is filled with the clear, proteinaceous colloid which contains large amount of thyroglobulin(Tg), the protein precursor of thyroid hormone and is normally the major constituent of the total thyroid mass. On cross-section, thyroid tissue appears as closely packed, ring-shaped lumen structures. The diameter of the follicles varies considerable, even within a single gland, but averages about 200 nm.

The follicular cells vary in height with the degree of glandular stimulation, becoming columnar when active and cuboidal when inactive. The epithelium rests on a basement membrane that is rich with glycoproteins and separates the follicular cells from the surrounding capillaries. Between 20 and 40 follicles are demarcated by connective tissue septa to form a lobule supplied by a single artery. From the apex of the follicular cell, numerous microvilli extend into the colloid. It is at or near this surface of the cell that iodination, exocytosis, and hormone secretion "colloid resorption" occur. The cytoplasm contains an extensive endoplasmic reticulum (ER) laden with microsomes. The ER is composed of a network of wide, irregular tubules that contain the precursor of Tg. The carbohydrate component of Tg is added to this precursor in the Golgi apparatus, which is located apically. Lysosomes and mitochondria are scattered throughout the cytoplasm. Stimulation by TSH results in enlargement of the Golgi apparatus, formation of pseudopodia at the apical surface, and the appearance in the apical portion of the cell of many droplets that contain colloid taken up from the follicular lumen these undergo proteolysis within the cell to yield thyroid hormones for secretion in to the bloodstream.[11&12]

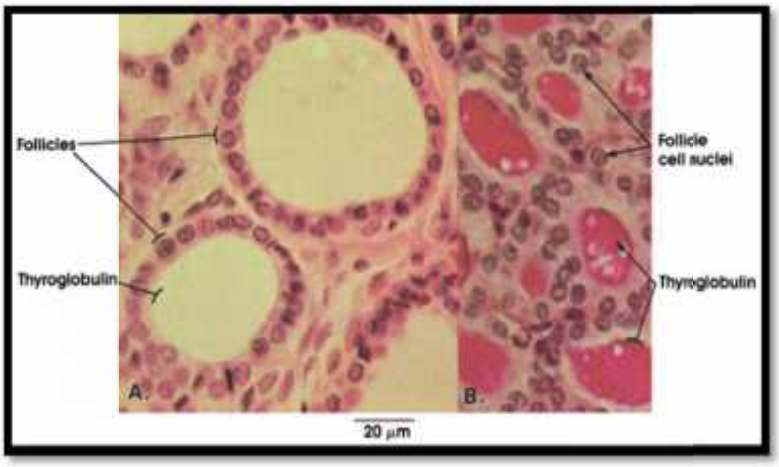


Fig.2-Microscopy of Thyroid Gland

THE THYROID HORMONES-CHEMISTRY

Thyroid gland secretes-

Iodothyronines-secreted by follicular cells

Calcitonin-secreted by parafollicular cells

The term iodothyronines means two hormones.

3,5,3',5' tetraiodothyronine or Thyroxine, which is abbreviated as T4

3,5,3' triiodothyronine, which is abbreviated as T3.

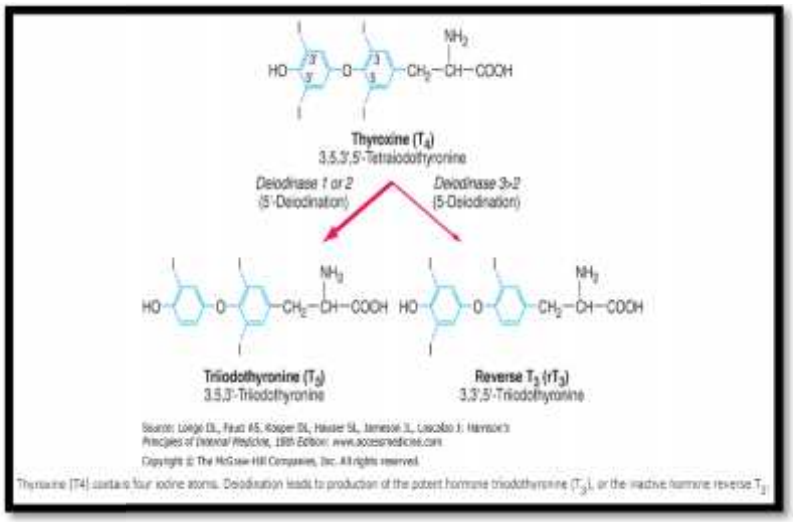


Fig:3 –molecular structures of T3 and T4

IODINE IS REQUIRED FOR THE FORMATION OF THYROXINE:

To form normal quantities of thyroxine, about 50mg of ingested iodine in the form of iodides are required each year, or about 1mg/week. To prevent iodine deficiency, common table salt is iodized with about 1 part sodium iodide to every 100,000 parts sodium chloride.[13]

FATE OF INGESTED IODIDES:

Iodides ingested orally are absorbed from the gastro-intestinal tract into the blood in about the same manner as chlorides. Most of the iodides are rapidly excreted by the kidney, but only after about one fifth are selectively removed from the circulating blood by the cells of the thyroid gland and used for synthesis of thyroid hormones.[13]

IODIDE TRAPPING (IODIDE PUMP):

Food iodide from the blood is taken up by the follicular cells of thyroid- a process called iodide trapping. Iodide trapping occurs against electrochemical gradient because the interior of the follicular cells is –ve and iodide ion is also –ve. The Iodide concentration of follicular cells is 30 times higher than in the blood hence, iodide trapping is a active process requires the activity of $Na^{+}K^{+}$ATPase. When the thyroid gland becomes maximally active, this concentration ratio can rise to as high as 250times.[13]

The rate of iodide trapping is influenced by several factors, the most important being the concentration of TSH; TSH stimulates and hypophysectomy greatly diminishes the activity of iodide pump in the thyroid cells.[13]

THYROID HORMONE BIOSYNTHESIS

OXIDATION OF IODIDE ION:

The first essential step in the formation of the thyroid hormones is conversion of iodide ions to an oxidized form of iodine, which is then capable of combining directly with amino acid thyrosine. This oxidation of iodine is promoted by the enzyme peroxidase and its accompanying hydrogen peroxide, which provides potent system capable of oxidizing iodides. The peroxidase is either located in the apical membrane of the cell or attached to it, thus providing the oxidized iodine at exactly the point in the cell where the thyroglobulin molecule issues forth from the golgi apparatus and through the cell membrane into the stored thyroid gland colloid. When the peroxidase system is blocked or when it is hereditary absent from the cells, the rate of formation of thyroid hormone falls to zero.[13]

IODINATION OF TYROSINE AND FORMATION OF THYROID HORMONES- "ORGANIFICATION OF THYROGLOBULIN":

The binding of iodine to thyroglobulin molecule is called as organification of the thyroglobulin. The oxidized iodine is associated with an iodinase enzyme that causes the process to occur within seconds or minutes. Thyrosine is first iodized to monoiodotyrosine and then to diiodothyrosine. Then iodotyrosine residues become coupled with one another.[13]

The major hormonal product of coupling reaction is the molecule thyroxine that remains part of thyroglobulin molecule or one molecule of monoiodothyrosine couples with one molecule of diiodotyrosine, which represents about one fifteenth of final hormones.[13]

STORAGE OF THYROGLOBULIN:

The thyroid gland is unusual among the endocrine glands in its ability to store large amounts of hormone. After synthesis of thyroid hormones has run its course, each thyroglibulin molecule contains upto 30 thyroxine molecules and a few triiodotyrosine molecules. In this form the thyroid hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months. Therefore, when synthesis of thyroid hormone ceases, the physiologic effects of deficiency are not observed for several months.[13]

RELEASE:

Thyroglobulin itself is not released in to the circulating blood in measurable amounts; instead, thyroxine and triiodothyronine must first be cleaved from thyroglobulin molecule, and then these free hormones are released. This process occurs as follows: the apical surface of the thyroid cells send out pseudopod extensions that close around small portions of colloid to form pinocytic vesicles that enter the apex of the thyroid cell. Then lysosomes in the cell cytoplasm immediately fuse with these vesicles containing digestive enzymes from the lysosomes mixed with the colloid. Multiple proteases among the enzymes digest the thyroglobulin molecules and release thyroxine and triiodothyronine in free forms. These are then released in to the blood.[13]

About three quarters of the iodinated tyrosine in the thyroglobulin never becomes thyroid hormones but remains the same and they are not secreted into the blood. Instead their iodine is cleaved from them by diiodinase enzyme that makes virtually all this iodine available again for recycling within the gland for formation

of additional thyroid hormones. In congenital absence of this diiodinase enzyme, the person becomes iodine deficient because of failure of the recycling process.[13]

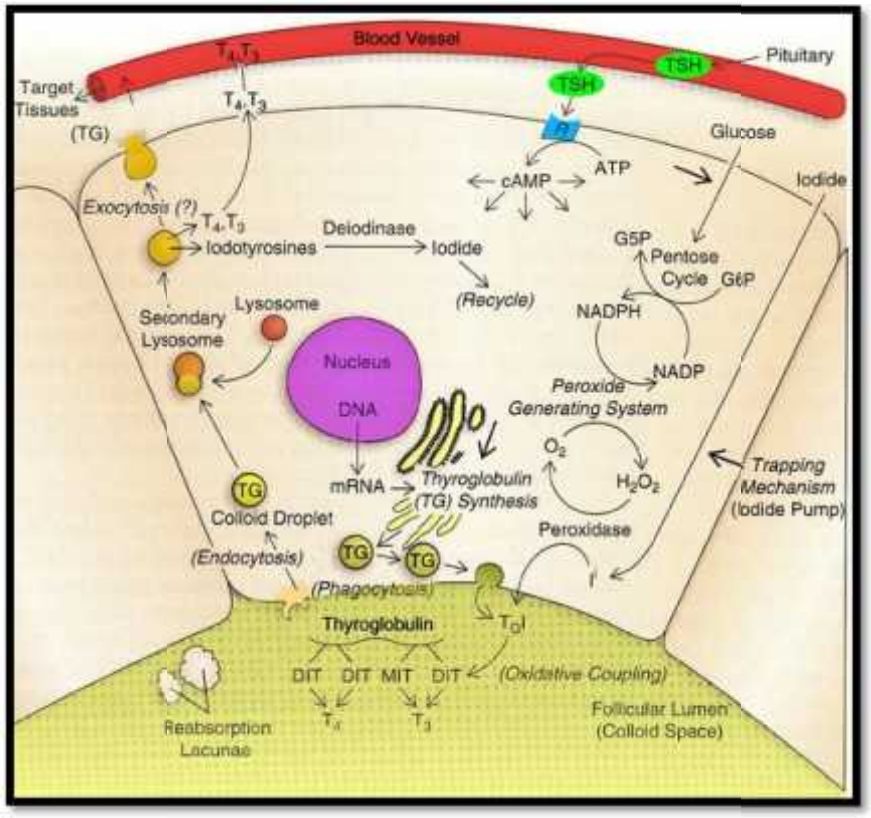


Fig4: Biosynthesis of Thyroid hormone

TRANSPORT IN THE BLOOD:

Over 99% of T4 and T3 are bound to plasma proteins and less than 1% is unbound (free).But this unbound fraction alone can combine with their receptors to perform the thyroid hormone functions and subsequently degraded. The bound fraction serves as reservoir. When the free fraction is diminished, a portion of the bound fraction becomes unbound to replenish the free fraction. Three plasma proteins, all synthesized in the liver bind with iodothyronines.[13]

- Throxine bindling globulin (TBG), which carries 75% of T4 and T3
- Albumin
- Thyroxine binding prealbumin (TBPA) also called transthretin which preferentially carries T4.

CONTROL OF THYROID SECRETION:

Secretion of the thyroid hormones depends upon two major factors:

1. HPT (hypothalamus-pitutary-thyroid)axis
2. Negative feedback mechanism

HPT AXIS:

Median eminence of hypothalamus secretes TRH (Thyrotropin releasing hormones), a bipeptide with molecular weight 28,000 daltons.TRH stimulates the thyrotrophs of anterior pituitary to secrete and release TSH (thyroid stimulating hormone).TSH stimulates the follicular cells of thyroid gland and regulates every step of thyroid hormone synthesis. The ability of TSH to trap iodide depends to some extent on the blood iodide concentration. If the concentration of blood iodine is high (eg : high iodine intake), despite the presence of adequate TSH, iodide trapping by follicular cells is poor. If the food iodine intake is very low, TSH causes increased iodide trapping.

NEGATIVE FEEDBACK:

If food iodide content is very low, little or no T4 is formed, owing to negative feedback mechanism, TSH secretion increases leading to goiter and this condition is called as iodine deficiency goiter. When the serum concentration of T4 and T3 is very low(hypothyroidism) the serum concentration of TSH, owning to the negative

feedback mechanism should be very high. Conversely, when there is high T4 and T3 in the serum , the TSH concentration of serum should be very low or nil (hyperthyroidism).

EFFECTS OF TSH:[13]

- Increased proteolysis of thyroglobulin.
- Increased activity of iodine pump
- Increased iodination of tyrosine
- Increased size and increased secretary activity of the thyroid cells
- Increased number of thyroid cells

HYPOTHYROIDISM AND INFERTILITY

Thyroid function and prolactin are closely interrelated. Long-standing, untreated hypothyroidism is associated with ovulatory dysfunction and, in 1–3% of cases, with galactorrhoea. Increased thyrotrophin releasing hormone (TRH) production, or more likely a diminished hypothalamic dopamine turnover , account for hyper secretion of thyroid-stimulating hormone (TSH) and prolactin in hypothyroidism. Hypothalamic deficiency of dopamine not only explains the prolactin and TSH abnormalities, but also increased luteinizing hormone (LH) overproduction. Disturbed pulsaile release of LH, TSH and prolactin interferes with the normal hypothalamic-pituitary–ovarian function. This can result in menstrual dysfunction, ranging from inadequate corpus luteum progesterone secretion to oligomenorrhoea or amenorrhoea. Subclinical hypothyroidism can be an early stage of hypothyroidism and is characterized by an exaggerated TSH. Subclinical hypothyroidism has also been reported in a cohort of women with premenstrual syndrome.

THYROID FUNCTION AND ITS SIZE IN PREGNANCY AND AFTER DELIVERY:

IODINE IN PREGNANCY AND AFTER DELIVERY:

Iodine metabolism:

Iodine metabolism in pregnancy is marked by several characteristics. Synthesis of thyroid hormones is increased by up to 50% due to estrogen induced increase in TBG concentration. Renal clearance of iodide increases owing to higher glomerular filtration rate. Iodide and iodothyronines are transported from maternal circulation to fetus.[18]Fetal thyroid hormone production increases during second half of gestation and after delivery. Iodide is also transported into the breast milk.[18]

Iodine supply:

According to Endocrine Society Clinical Practice Guidelines, Iodine intake before pregnancy should be 150µg/day in order to maintain adequate intrathyroidal iodine stores. During pregnancy and lactation, the recommended iodine intake is 250µg/day. When evaluating adequacy of iodine supply in pregnant women, urinary iodine concentration, as a measure of iodine supply should be in the light of the fact that volume of daily urine usually totals 1.5liters and approximately 10% of iodine is not excreted via urine.[19]Iodine deficiency several metabolic changes and goiter in the mother and fetus.[18]In mild iodine deficiency , leads to lower levels of fT4 & fT3 and higher levels of TSH, TBG, thyroglobulin were observed in the second and third trimester of pregnancy when compared with first trimester. In the third trimester maternal thyroid volume was also larger[20].

MATERNAL THYROID FUNCTION:

Transport protein:

Besides TBG, which is the major thyroid hormone transporter proteins, transthyretin and albumin are also important. The level of albumin, which has lowest thyroxine affinity and enables a fast release of T4, gradually decrease during pregnancy[18&21.]TBG is an active carrier and has a possibility to switch between high affinity and low affinity forms[22]. The TBG levels are highest in the second and third trimester of pregnancy[20] and the same holds true for thyroid hormone binding ratios[23] and thyroid binding capacity [24], which decreases as soon as 3-4 days after delivery. In pregnancy TBG production in the liver is increased and half life of TBG is prolonged because of estrogen induced increase in sialylation on TBG, therefore half life of TBG is increased from 15min to 3days[18].

Variation in HCG:

HCG has intrinsic thyrotropic activity. It increases shortly after conception, peaks around gestational age week 10, declines to a nadir by week 20.[18]It directly activates TSH receptor. Transient decrease in TSH between 8-14weeks mirrors the peak HCG concentration. In 20% of normal pregnant women TSH level decreases to less than lower limit of normal.

During the first trimester of pregnancy, 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.[20]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. Members of the glycoprotein hormone family of luteinizing hormone, follicle stimulating hormone,

TSH, and hCG contain a common α-subunit and a hormone specific β sub unit. Because the hCG and TSH β sub units share 85% sequence homology in the first 114 amino acids and contain 12 cysteine residues at highly conserved positions, it is likely that their tertiary structures are very similar.[25&26]

Purified hCG . Like TSH, has been shown to induce the following changes in experimental setups

(a) Increase iodine uptake and cAMP production in FRTL-5 rat thyroid cells

(b) Increase cAMP production dose dependently and displace binding of 125 iodine-labeled TSH in Chinese Hamster ovary cells stably transfected with human TSH receptor and

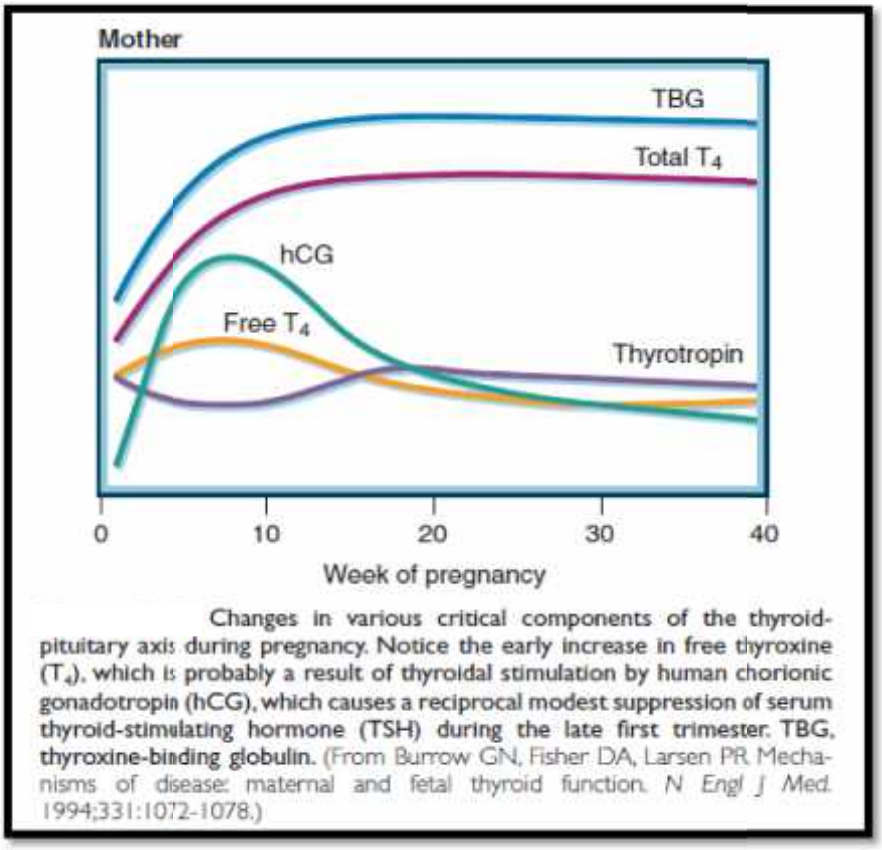
(c) Stimulate iodide uptake, organification and T3 secretion in cultured human thyroid follicles[25&26]

It has estimated a 10,000IU/L increment in circulating hCG corresponds to a mean free T4 increment in serum of 0.6pmol/L(0.1ng/dL) and in turn, to a lowering of serum TSH of 0.1mIU/L.[18]Hence ,it is predicted that an increase in serum free T4 during the 1st trimester will be observed only when hCG concentrations of 50,000-75,000 IU/L are maintained for >1week.[26]

Variations in TSH:

Most authors agree that in the first trimester, TSH levels may be decreased in some women with otherwise healthy thyroid gland. During pregnancy, TSH level increases and reach the highest value in the third trimester, irrespective of iodine supply[20]. After 3-4days after delivery, TSH levels were the highest[24]. Higher TSH levels in second half of pregnancy probably mirrors HCG and free thyroid hormones levels, being lower in that period of pregnancy.Four months after delivery, TSH

level were lower than in third trimester[28]. After one year postpartum they were lower than in the second and third trimester[18].



Changes in various critical components of the thyroid-pituitary axis during pregnancy. Notice the early increase in free thyroxine (T_4), which is probably a result of thyroidal stimulation by human chorionic gonadotropin (hCG), which causes a reciprocal modest suppression of serum thyroid-stimulating hormone (TSH) during the late first trimester. TBG, thyroxine-binding globulin. (From Burrow GN, Fisher DA, Larsen PR. Mechanisms of disease: maternal and fetal thyroid function. *N Engl J Med.* 1994;331:1072-1078.)

Fig: 5 Hormonal variations in the mother

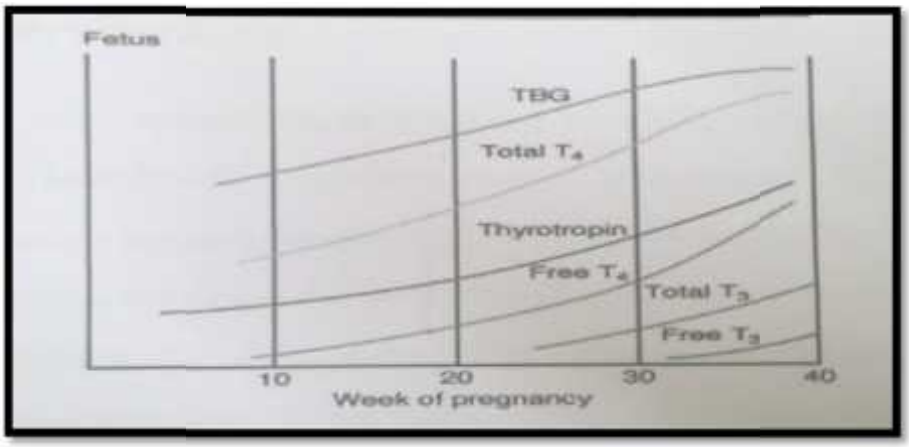


Fig: 6: Hormonal variation in the fetus

PHYSIOLOGICAL CHANGE	RESULTING CHANGES IN THYROID ACTIVITY
⇧ Serum estrogen	⇧ Serum TBG
⇧ Serum TBG	⇧ Demand for T4 and T3 ⇧ In total T4 and T3
⇧ hCG	⇩TSH(In reference range unless hCG >50000 IU/L ⇧fT4 (in reference range unless hCG >50,000IU/L
⇧ Iodine clearance	⇧In dietary requirement for I^- ⇩ In hormone production in I^- deficient areas ⇧ Goiter in I^- deficient areas
⇧ Type III deiodinase	⇧ T4 and T3 degradation ⇧Demand for T4 and T3
⇧ Demand for T4 and T3	⇧Serum thyroglobulin ⇧ Thyroid volume ⇧Goiter in iodide deficient areas

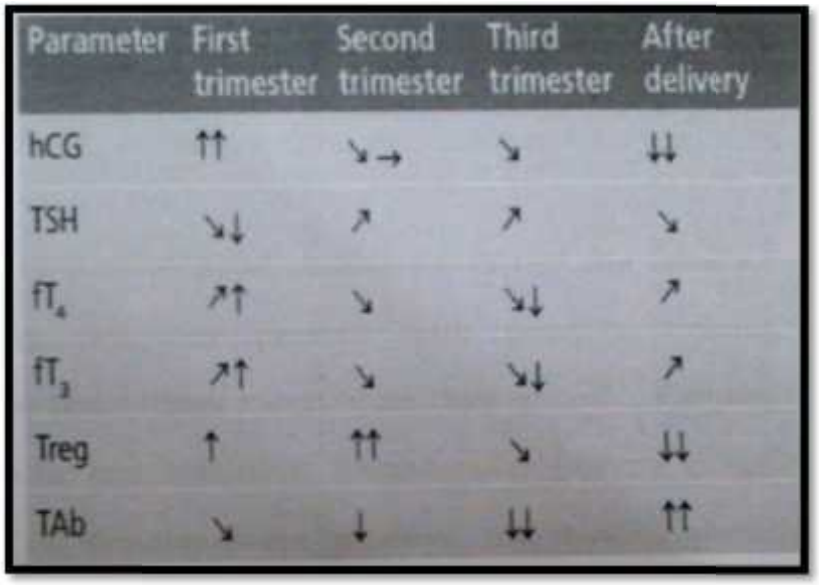
Variations in free thyroid hormones:

Even in areas with adequate iodine intake, many authors established pregnancy levels of the FT4 and FT3 to be lower than in non-pregnant individuals. In the last months of pregnancy, FT4 levels were often below the reference interval. Free thyroxine is slightly increased in the first trimester and decreased by approximately 30% to low normal values in second and third trimester[19]. Several factors may influence the level of free thyroid hormones. Increased hCG at 1l-l3wks was associated with increased median values of FT4[30]. Twin pregnancies with higher hCG values of longer duration frequently lead to increased FT4[18].

Maternal thyroid size:

Thyroid size is influenced by different factors, including iodine supply, genetics, gender, age, TSH, anthropometric parameters, parity and smoking[31]. In areas with adequate iodine intake, thyroid volume did not change during pregnancy[32]. The increase in thyroid volume during pregnancy was followed by the decrease after delivery and on the basis of this finding it was postulated that increased vascularity may be the reason for the increase in thyroid volume[18].

THYROID AUTOIMMUNE DISEASE IN PREGNANCY & AFTER DELIVERY



Parameter	First trimester	Second trimester	Third trimester	After delivery
hCG	↑↑	↘→	↘	↓↓
TSH	↘↓	↗	↗	↘
fT_4	↗↑	↘	↘↓	↗
fT_3	↗↑	↘	↘↓	↗
Treg	↑	↑↑	↘	↓↓
TAb	↘	↓	↓↓	↑↑

Fig. 7 - Thyroid physiology and autoimmunity in pregnancy and after delivery

-: No change; ↘: Slight decrease; ↓: Decrease; ↓↓: Marked decrease; ↗: Slight increase; ↑: Increase; ↑↑: Marked increase when compared with the previous period.

FT3: Free triiodothyronine; FT4: Free thyroxine; hCG: Human chorionic gonadotropin; TAb: Thyroid autoantibodies; TSH: Thyroid stimulating hormone.

Graves' disease (GD):

In females in the reproductive period, GD is the most frequent cause of hyperthyroidism, which occurs in the population with an estimated prevalence of approximately 1%[37]. Among pregnant women the prevalence rate of overt hyperthyroidism is approximately 0.1-0.4% and GD accounts for 85-90% of all cases[53]. In this type of thyroid autoimmunity, the humoral immune response predominates with the characteristic appearance of stimulating antibodies against TSH receptor (TRAbs), causing hyperthyroidism, goiter and nonthyroid manifestations, such as Graves' orbitopathy or dermopathy.

Owing to physiological immunosuppression during pregnancy, the development of GD or relapse of hyperthyroidism in this period is rare, usually emerging in the first trimester of pregnancy. In the second half of pregnancy even the gradual improvement of previously existing hyperthyroidism is frequently observed, being most probably the reflection of the stimulating TRAbs decrease in the second and third trimester[54].

In the postpartum period, when the immunosuppression ceases, the increase of stimulating TRAbs[55], together with relapse of GD, is frequently observed, usually between 4 and 8 months after delivery. In the recent study of patients in remission after antithyroid drug treatment, the recurrence of GD was determined in 84% of patients in the postpartum period compared with only 56% of patients not being pregnant[56]. However, as indicated by one single study, the postpartum period itself has not been shown to be a major risk factor for the first onset of GD[57].

Untreated or inadequately treated GD in pregnancy may lead to several detrimental complications. In mothers, hyperthyroidism has been associated with preeclampsia and with the increased risk of congestive heart failure and thyroid storm. In the pregnancy course, hyperthyroidism may increase the risk of miscarriage, stillbirth, preterm delivery and placental abruption.

Fetal hyperthyroidism, which occurs in less than 0.01 % of pregnancies[58] may lead to tachycardia, fetal goiter,congenital malformations, accelerated bone maturation, growth retardation and low birth weight. In the fetus, the excess of thyroid hormones may be the reflection of the mother's thyroid hormones or the mother's stimulating TRAbs crossing the placenta. Those antibodies have the impact on fetus only after the twelfth week of gestation, when the fetal thyroid starts to

respond to the stimulation[46]. In late pregnancy they represent a risk of neonatal hyperthyroidism, which occurs in up to 5% of newborns of mothers with GD. It usually persists for up to 12 weeks due to slow clearance of maternal antibodies, having a half-life of approximately 3 weeks[54].

Hashimoto's thyroiditis(HT):

With the estimated prevalence of 18% in the population, HT is probably one of the most prevalent autoimmune disorders in general. In women during the reproductive period, the prevalence of thyroid antibodies was approximately 10-15% and the prevalence increased with age[37].In contrast to GD, in HT the cell-mediated immune response predominates with consequent gradual destruction of thyroid tissue, which frequently leads to hypothyroidism. In pregnancy, the TPOAb and TgAb were shown to decline gradually with the lowest values in the third trimester, while the increase was observed as soon as 6 weeks after delivery and returning to the prepregnant values 12 weeks after[33.]

In HT, both hypothyroidism and thyroid autoantibodies have been implicated to be involved in pregnancy complications. Overt or subclinical hypothyroidism, occurring in approximately 2-4% of apparently healthy women, has been related to two- three fold increased risk of gestational hypertension, placental abruption, postpartum hemorrhage, preterm delivery or miscarriage.

Besides increased risk of low birth weight, neonatal respiratory distress and fetal abnormalities, such as hydrocephalus and hypospadias, maternal hypothyroidism during pregnancy has also been demonstrated to affect neuropsychological development of the child[13].However, rapid and adequate

correction of hypothyroidism with L-thyroxine therapy has been shown to improve obstetrical outcome[18].In euthyroid pregnant women, elevated thyroid autoantibodies have been associated with two-to four-fold increased risk of miscarriage and with up to threefold increased risk of preterm delivery, although the etiology remains unresolved. Those complications may be associated with underlying generalized immune imbalance, with subtle deficiency of thyroid hormones due to thyroid autoimmunity, or with older age of those women[18].

Hypothyroidism may also lead to infertility, since menstrual disorders, including oligomenorrhea, menorrhagia and ovulatory dysfunction may occur and their severity correlates with the elevation of serum TSH levels. Similarly hypothyroidism may provoke in vitro fertilization failure in infertile females, while L-thyroxine replacement has been shown to improve embryo implantation rate and pregnancy outcome. However, the clinical importance of thyroid antibodies in infertility remains controversial and underlying pathogenic mechanisms of putative association still need to be clarified[18].

Postpartum thyroiditis(PPT):

Postpartum thyroiditis refers to thyroid dysfunction within the first year after delivery or miscarriage, when the known immunosuppressive effect of pregnancy disappears. The clinical disease may present with hyperthyroidism alone, only with hypothyroidism, or with hyperthyroidism followed by hypothyroidism. The prevalence varies significantly between studies from 1.1 to 21.1% with estimated pooled prevalence in the general population of approximately 8%, occurring up to six times more often in women with elevated TPOAb and three times more often in

females with Type 1 diabetes[59].Therefore, in these two groups screening for thyroid dysfunction is recommended 3 and 6 months after delivery[18].

Females positive for TPOAb in early pregnancy develop PPT in 40-60% of cases, while among patients with PPT 70% present with positive TPOAb, putting them at risk for developing a permanent thyroid dysfunction[33]. The hyperthyroid phase of the disease is only transient, more frequently occurring in TPOAb-negative patients between 1 and 6 months after delivery and lasting 1-2 months. Hypothyroidism may occur with or without a previous hyperthyroid phase, more often in TPOAb-positive patients and between 3 and 8 months after delivery, being caused by destruction of thyroid tissue[33]. It may be only transient, lasting 4-6 months and passing within 1 year after delivery or it may be permanent[18]. A few earlier studies reported permanent hypothyroidism in up to 30% of PPT patients[18], but a recent large prospective report demonstrated a significantly higher incidence of approximately 50%. The latter observation might be an overestimation, since owing to limited sampling only 6 and 12 months after delivery a considerable number of patients with transient hypothyroidism may have been missed[60].

However, patients with transient hypothyroidism are also at risk for developing permanent hypothyroidism, which is established within 5-10 years after post partum thyroiditis in 20-60% of women[59]. While in the hyperthyroid phase no specific antithyroid therapy is indicated, replacement therapy with L-thyroxine frequently needs to be started in hypothyroid patients[18].

LABORATORY DIAGNOSTIC CRITERIA FOR HYPOTHYROIDISM IN PREGNANCY

Overt hypothyroidism is defined as an elevated TSH (>2.5 mIU/L) in conjunction with a decreased FT4 concentration. Women with TSH levels of 10.0mIU/L or above, irrespective of their FT4 levels, are also considered to have overt hypothyroidism[92].

Subclinical hypothyroidism is defined as a serum TSH between 2.5 and 10 mIU/L with a normal FT4 concentration.[92].

Untreated hypothyroidism is associated with pregnancy induced hypertension, abruption placenta, postpartum hemorrhage, premature birth, low birth weight infants and impaired neurodevelopment in offspring[26].

American thyroid association (2007) recommends cut off values for TSH as,

- First trimester - < 2.5mIU/L
- Second & third trimester - <3 mIU/L
- Lower limit of normal — 0.04 mIU/L

ETIOLOGY OF HYPOTHYROIDISM IN PREGNANCY:[18&26]

1. Hashimoto disease.
2. Post thyroid ablation/removal
3. Iodine deficiency.
4. Primary atrophic hypothyroidism.
5. Infiltrative disease.(eg: sarcoidosis, amylodosis).
6. TSH dependent hypothyroidism.

CLINICAL DIAGNOSIS OF HYPOTHYROIDISM:

Clinical signs and symptoms[26]

- Low energy.
- Inappropriate weight gain.
- Constipation.
- Goiter.
- Cold intolerance.
- Low pulse rate

Laboratory assessment of hypothyroidism must be made using TSH and free hormone levels assessment. Total T3 &T4 measurements should be considered unreliable because of increase in TBG concentration. Anti TPO antibodies and anti thyroglobulin antibodies are increased in most patients of hashimotos thyroiditis & therefore help in diagnosis. In addition pregnant women who are on thyroid replacement therapy require larger doses compared to non pregnant patients because of increase in TBG concentration & increase in type 3 deiodinases from the placenta. TSH should be monitored closely and the doses of thyroid replacement to be adjusted to maintain TSH with in reference range. Doses of thyroid replacement therapy can be lowered to pre pregnancy levels at parturition.[26]

MANAGEMENT:

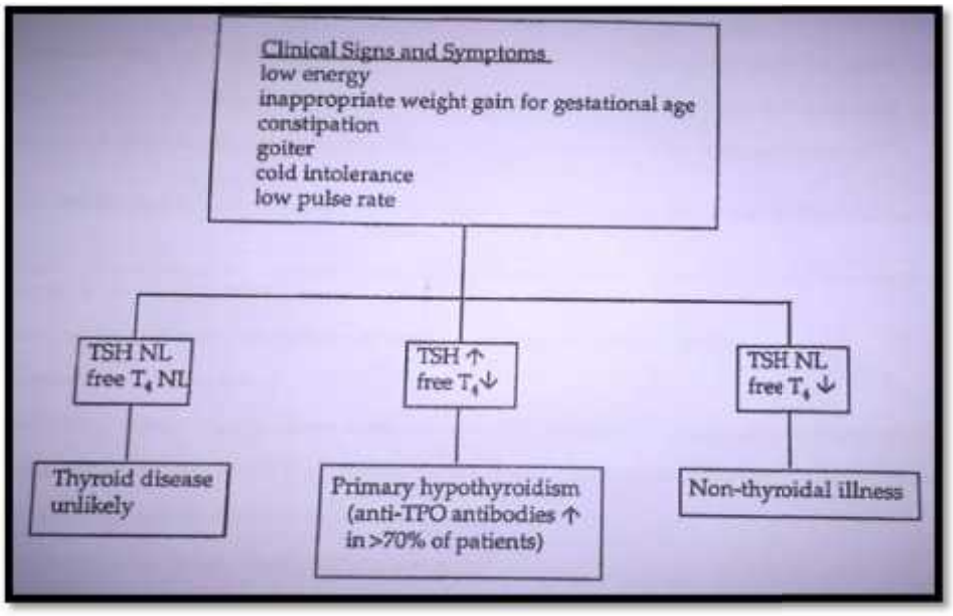


Fig:8 Algorithm for the evaluation of hypothyroidism during pregnancy.

NL-with in reference interval, ↑increased ,↓decrease

The starting dose of levothyroxine is 1-2µg/kg/day. It should be adjusted every 4 weeks to keep TSH at lower end of normal. Women who are on levothyroxine at the beginning of pregnancy should have their dose increased approximately 30% as soon as pregnancy is confirmed. Levothyroxine & ferrous sulfate doses should be spaced at least 4 hours apart, to prevent inadequate intestinal absorption of levothyroxine.[66]

FOLLOW UP AFTER DELIVERY:

After delivery, levothyroxine therapy should be returned to prepregnancy dose, and TSH checked 8wks postpartum. Breastfeeding is not contraindicated in women treated for hypothyroidism. Levothyroxine is excreted in breast milk, but the

levels are too low to alter thyroid function in the infant. Periodic monitoring with an annual serum TSH concentration for the mothers is generally recommended.[67]

Causes Of Raised TSH activity in patients receiving standard replacement

doses Of Levothyroxine[68]

- Non - compliance - supervised administration of standard daily or single weekly dose of 1000µg
- Inadequate dose - dispensing error, change in formulation
- Interaction with drugs
- Reduced absorption-Iron tablets, cholestyramine, calcium carbonate, Soya
- Rapid clearance of Levothyroxine in patients on Phenytoin, Carbamazepine, Rifampcin , Valproate
- Residual gland dysfunction
- Autoimmune, post-irradiation, surgery
- Pregnancy
- Postmenopausal oestrogen treatment (increase in TBG concentrations)
- Systemic illness

RECOMMENDATIONS [69]

- Trimester and population specific reference ranges for TSH should be applied. If they are not available in the laboratory, the following reference ranges are recommended: first trimester 0.1-2.5mIU/L; second trimester 0.2—3.0mIU/L; third trimester 0.3—3.0mIU/L.
- Method-specific and trimester-specific reference ranges of serum FT4 are required.

- All women with hypothyroidism and women with subclinical hypothyroidism who are positive for TPOAb should be treated with levothyroxine(LT4), however due to the lack of randomized controlled trials there is insufficient evidence to recommend for or against universal LT4 treatment in TPOAb negative pregnant women with subclinical hypothyroidism.
- The goal of LT4 treatment is to normalize maternal serum TSH values within the trimester-specific pregnancy reference range.
- LT4 dose should be increased by 25-30% upon a missed menstrual cycle or positive home pregnancy test. This adjustment can be accomplished by increasing LT4 by additional 2 tablets of LT4 per week. Further adjustments should be individualized as they are dependent on the etiology of maternal hypothyroidism, as well as the preconception level of TSH. Serum thyroid function tests should be monitored closely.
- Hypothyroid patients on treatment with LT4 who are planning pregnancy should have their dose adjusted by their provider in order to optimize serum TSH values to <2.5 mIU/L preconception.

In 2010 Sahu, Meenakshi Titoria et al, screened 633 pregnant women in second trimester. TSH level estimated. If TSH level was deranged, then free T4 and Thyroperoxidase antibody level were done. Patients were managed accordingly and followed till delivery. Their obstetrical and perinatal outcomes were noted. Their results showed that prevalence of thyroid dysfunction was high , with subclinical hypothyroidism in 6.47% and overt hypothyroidism in 4.58% women.[6]Overt hypothyroids were prone to have pregnancy induced hypertension (P = 0.04) . Intrauterine growth restriction (P = 0.01) and intra uterine demise (P = 0.0004) as compared to control. CS rate for fetal distress was significantly higher among

pregnant subclinical hypothyroid women. (P = 0.04). Neonatal complications and gestational diabetes were significantly more in overt hyperthyroidism group (P=0.03 and P = 0.04) respectively. They concluded that prevalence of thyroid disorders, especially overt and subclinical hypothyroidism (6.47%) was high. Significant adverse effect on maternal and fetal outcome were seen emphasizing the importance of routine antenatal thyroid screening.[74]

In 2005, Casey BM et al Parkland hospital USA, screened a total of 25,756 women for thyroid status who delivered Singelton infants. There were 17298 (67%) women enrolled for prenatal care at 20 weeks gestation or less, and 404 (23%) of these were considered to have subclinical hypothyroidism. Pregnancies in women with subclinical hypothyroidism were 3 times more likely to be complicated by placental abruption (RR-3.O, 95% confidence interval 1.1-8.2). Preterm birth, defined as a delivery at or before 34 weeks of gestation was almost 2- fold higher, in women with subclinical hypothyroidsm (RR 1.8, 95% confidence interval 1.1-2.9) [77]

In 1998, study was done by Leung AS et al LosAngeles. A cohort of 68 hypothyroid patients with no other medical illness was divided in to two groups according to thyroid function tests. The first one had 23 women with overt hypothyroidism and the second 45 women with subclinical hypothyroidism. They sought to identify the pregnancy outcomes. Pregnancy induced hypertension- namely Eclampsia, Preedampsia and Gestational hypertension was significantly more in overt and subclinical hypothyroidism patients in the general population with rates of 22.1 5 and 7.6% respectively. In addition 36% of the overt, and 25% of the subclinical hypothyroid subjects, who remained hypothyroid at delivery developed

gestational hypertension, Except for one still birth and one case of club feet, Hypothyroidism was not associated with adverse fetal and neonatal outcome.[76]

In the year 2006, BijayVaidya, Exeter hospital, UK, prospectively analyzed TSH, FT4 , FT3 in 1 560 consecutive pregnant women during their 1st antenatal visit (Median gestation 9 weeks). They tested thyroperoxidase antibodies in 1327. (85%) They classified 413 women (26.5%) who had personal h/o thyroid or other autoimmune disorder or a family h/o thyroid disorder as a high risk group. They examined whether testing only such high risk group would pick up most pregnant women with thyroid dysfunction.[77]

The results were 40 women (2.6%) had raised TSH (>4.2 IU I ml). The prevalence of raised TSH was higher in the high risk group (6.8 V/s 1% low risk group, RR 65, 95% confidence, interval (CI) 3.3 -12.6 P < 0.0001) presence of personal h/o thyroid disease (RR 12.2, 95% CI 6.8- 2.2) P < 0.0001) with other autoimmune disorder (RR 4.8 , 95% CI 1.3 - 18.2, P = 0.0016) . Thyroid peroxidose antibodies (RR 8.4, 95% CI 4.6 -15.3 P < 0.0001) and family h/o thyroid disorder (RR 3.4, 95% , CI 1.8 - 6.2, P < 0.0001) increased risk of raised TSH. However 12 of 40 women with raised TSH (30%) were in the low risk group.

They concluded that targeted thyroid function testing of only high risk group would alteast miss about 1/3rd of pregnant women with overt / subclinical hypothyroidism.[79]

A recent study(2010) on Indian pregnant women to assess the prevalence of thyroid disorders and its impact on pregnancy outcome by Sahu MT et-al, concluded that prevalence of thyroid disorders, especially overt and subclinical hypothyroidism

(6.47%) was high in Indian pregnant women. Significant adverse effects on maternal and fetal outcome were seen emphasizing the importance of routine antenatal thyroid screening.[6].

Another study on Asian Indian pregnant women by Nambiar et-al in 2011 concluded that the prevalence of Thyroid Autoimmunity (12.4%) & hypothyroidism (4.8%) was high in pregnant women. Both thyroid autoimmunity and hypothyroidism were significantly associated with miscarriage.[85]

METHODOLOGY

MATERIALS AND METHODS:

This study was conducted in Dept of obstetrics and gynaecology at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, KLE University's teaching hospital attached to Jawaharlal Nehru Medical College Belgaum

Study Design:

One year case-control study.

Study Period:

One year from January 2012 to December 2012.

Sample Size:

Sample size was calculated based on the following formula.

$$\text{Sample Size (n)} = \frac{2\,(Z\alpha + Z\beta)^2\,P}{(P_0 - P_1)^2}$$

$Z\alpha = 1.65$

$Z\beta = 0.84$

P1=1%

P2=6%

Power = 80%

$P = (P1 + P2)/2 = (1+6)/2 = 3.5\%$

$G = 100 - P\% = 96.5\%$

$$\text{Sample Size (n)} = \frac{2\,(1.65 + 0.84)^2\ 3.5 \times 96.5}{5^2}$$

n=167.5 = 170 in each group

inclusion criteria

Cases: Pregnant women with minimum of any one of the following pregnancy complications in the present pregnancy -

- Abortion
- Hyperemesis gravidarum
- Preterm delivery
- IUGR
- Preeclampsia/Gestational hypertension
- IUD
- Gestational diabetes
- Abruptio placenta.

Controls: Antenatal women with normal ongoing pregnancy with previous normal pregnancy outcome.(Where ever applicable)

Exclusion criteria

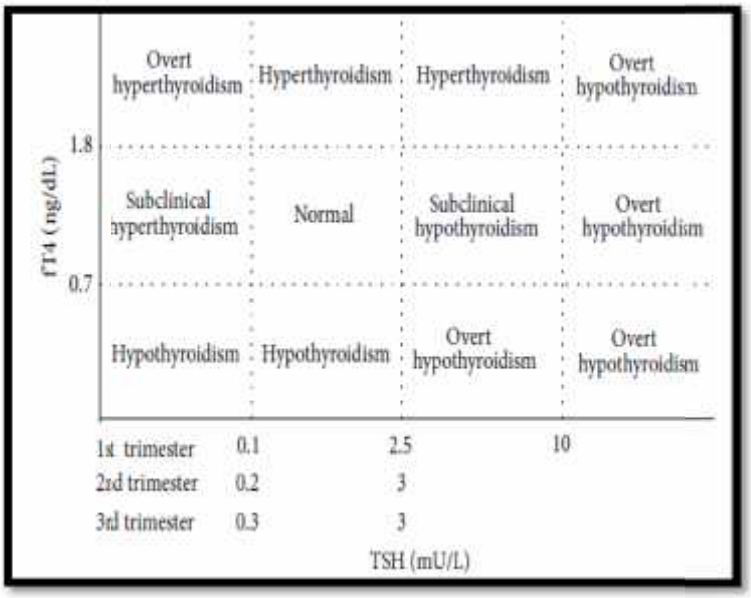
- Pregnant women with previously diagnosed thyroid dysfunction/ autoimmune disorders.
- A family history of thyroid dysfunction.
- Multiple pregnancy.
- Hyperthyroidism

Procedure:

Pregnant women with minimum of any one of the following pregnancy complications in the present pregnancy like spontaneous Abortion, hyperemesis gravidarum , Preterm delivery, IUGR, Preeclampsia/Gestational hypertension, Eclampsia, IUD, Gestational diabetes or Abruptio placenta are recruited as cases and pregnant women at similar gestational age with no previous or present pregnancy complication were recruited as controls.

Patient related information was collected and entered in to data collection instrument (Annexure II) after taking Informed written consent from the women from both cases and controls and they were subjected to testing of Sr.TSH, Free T3 and Free T4 levels only once. 2ml of blood samples was collected in a plain vaccutainer and sent to lab. At the laboratory FT3, FT4 & TSH and were estimated by the electro chemiluminescence immuno essay (CLIA) technique using commercially available kits analyzed in Siemens Centaur XP and the results were analyzed using :

1. Trimester specific cutoffs recommended by Thyroid Endocrine Society(TES)



2.Trimester specific cutoffs recommended for Indian pregnant women by RK Marwaha and et al that is the Indian reference range(IRR)

Table 2. Trimester-wise values for mean, median, 5th and 95th centiles for FT_3, FT_4 and TSH from reference population

	Trimesters	Mean ± SD	Median (range)	5th	95th
FT_3	I	4.36 ± 1.08	4.4 (0.37–6.58)	1.92	5.86
	II	4.34 ± 0.78	4.3 (2.7–7.69)	3.2	5.7
	III	4.15 ± 0.64	4.1 (2.93–5.92)	3.3	5.18
FT_4	I	14.9 ± 2.35	14.46 (8.04–22)	12	19.45
	II	14.0 ± 2.33	13.4 (9.26–22.12)	9.48	19.58
	III	13.76 ± 2.35	13.28 (9.54–27.02)	11.3	17.71
TSH	I	2.42 ± 1.65	2.1 (0.04–10.8)	0.6	5.0
	II	2.49 ± 1.9	2.4 (0.026–10.85)	0.435	5.78
	III	2.6 ± 1.9	2.1 (0.2–9.55)	0.74	5.7

FT_3: $P = 0.167$, NS; FT_4: $P = 0.0019$; TSH: $P = 0.641$, Not significant.
Comparison of FT_4: I vs II, $P = 0.015$; I vs III, $P = 0.003$; II vs III, P = Not significant.

All women cases and controls who had S.TSH levels below 0.1mIU/l in 1st ,0.2 mIU/l in 2nd and 0.3mIU/l in 3rd trimester were excluded from the study as they were diagnosed to be hyperthyroid.

The women who fulfilled the criteria below were labeled subclinical and overt hypothyroid accordingly:

Overt Hypothyroidism: is defined as an elevated TSH (>2.5 mIU/L) in conjunction with a decreased FT4 concentration. Or Women with TSH levels of 10.0mIU/L or above, irrespective of their FT4 levels, are also considered to have Overt hypothyroidism

Sub clinical hypothyroidism is defined as a serum TSH between

2.5 and 10 mIU/L with a normal FT4 concentration.[75]

The data is entered into a Microsoft Excel sheet and analyzed.

Statistical Analysis:

- Prevalence of Hypothyrodism in cases and controls by TES and IRR
- P value was found using chi square test
- Strength of association was found between cases and controls using Odd's ratio
- Strength of association was found between individual adverse pregnancy outcome and hypothyroidism using Odd's ratio.

RESULTS

This one year case control study and was conducted in the Department of Obstetrics and Gynecology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, KLE University's teaching hospital attached to Jawaharlal Nehru Medical College Belgaum, during the period from January 2012 to December 2012.

A total of 400 pregnant women attending antenatal clinic at OPD, admitted to maternity ward and Labour room were recruited in the study and grouped in to cases and controls by fulfilling the criteria of each of those groups. Both groups were screened for hypothyroidism by estimating S.TSH, Free T3 and free T4 levels. Based on the thyroid profile result, the cases and controls were further categorized in to Euthyroid, Subclinical hypothyroid and overt hypothyroid status based on TES and IRR trimester specific cut off values.

The data obtained was entered into Microsoft Excel Worksheet and the data was analyzed and results were tabulated as below.

Table 1. Age distribution

Age group (Years)	cases group (n=200)		Control Group (n=200)	
	Number	Percent	Number	Percent
< 20	22	11	36	18
20 to 25	107	53	91	45
26 to 30	54	27	57	28
> 30	17	9	16	9
Total	**200**	**100.00**	**200**	**100.00**

The mean age in cases group was 24.59 ± 4.14 years and the with range being 19 to 39 years. In control group the mean age was 24.74 ± 3.85 years and with range between 19 to 33 years.

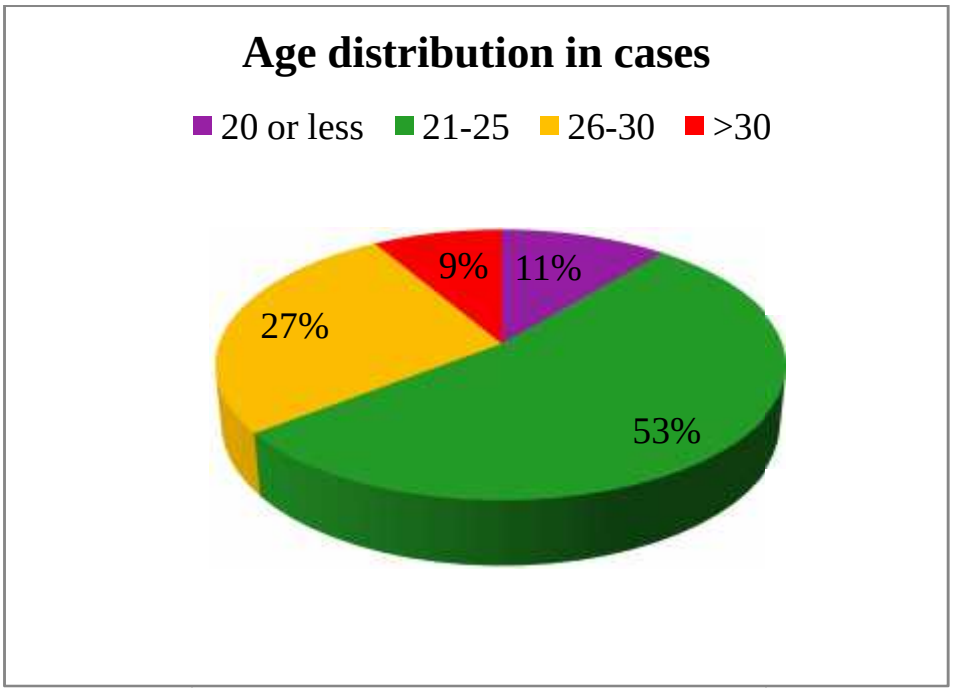
Most of the women in both these groups are in between 20 to 25years.

Table 2.Body Mass Index(BMI)

variables	control	cases
Mean height(cms)	154.85	151.63
Mean weight(kgs)	56.82	59.5
Mean BMI(kg/m^2)	23.7	24.81

It has been observed in this study that there is no much variation in the mean BMI between cases and controls.

Graph:1 Age distribution in cases and controls.



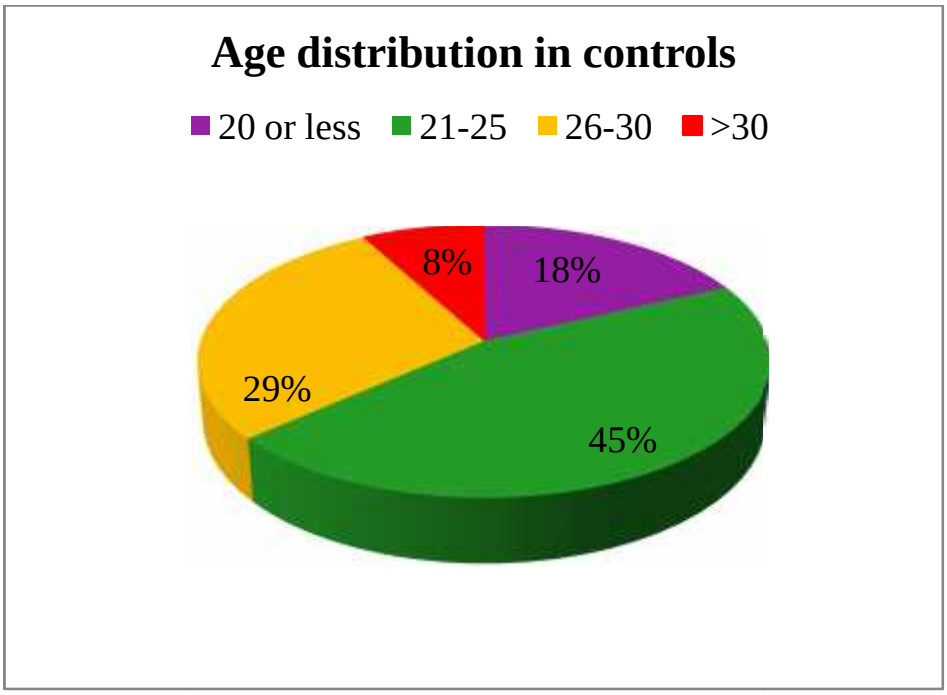
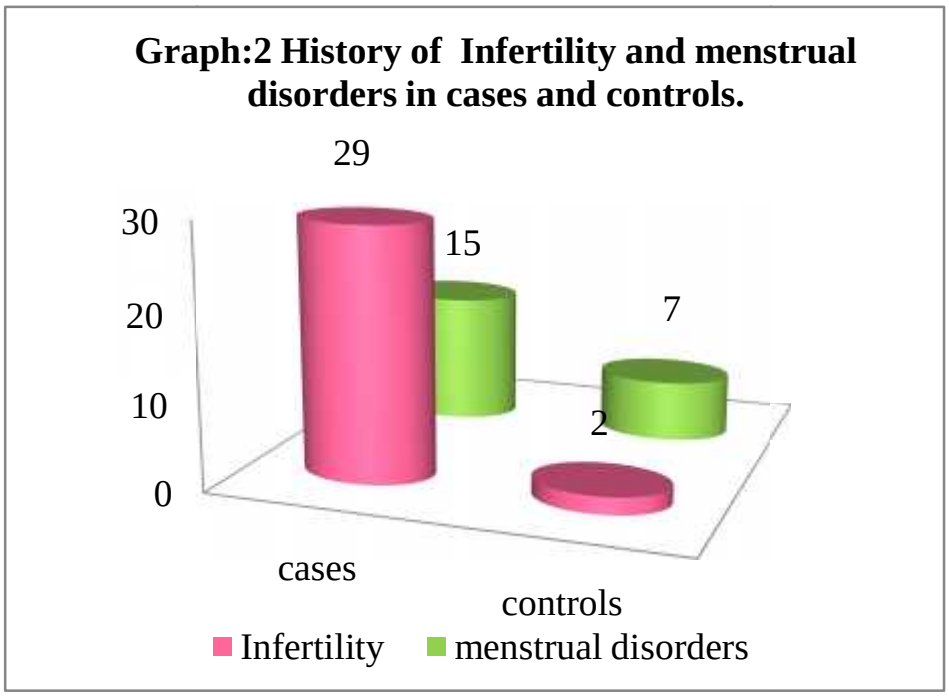


Table 3.History of Infertility and Menstrual disorders.

Parity	Cases		Control		P Value
	Number	Percent	Number	Percent	
History of Infertility	29	14.5	2	1	0.01
Menstrual disorders	15	7.5	7	3.5	0.07



It was observed that in 29 women among cases and 2 women among controls had history of Infertility The history of Infertility was significantly high among in cases than compared to controls with a P value of 0.01.

15 women had history of menstrual disorder among the cases and 7 in controls and history of menstrual irregularity was high among cases when compared to controls but not statistically significant.

Table 4.Trimester wise prevalence of Overt and Subclinical Hypothyroidism according to Thyroid Endocrine Society (TES)

T	Cases				Controls				
	n	SCH	OH	total	n	SCH	OH	total	P Value
I	41	18(43%)	3(7.3%)	21(51.2%)	41	6(14.6%)	0	6(14.6%)	0.003
II	40	9(22.5%)	1(2.5%)	10(25%)	40	2(5%)	0	2(5%)	0.002
III	119	51(42.8%)	17(14.2%)	68(57.1%)	119	8(6.7%)	0	8(6.7%)	0.001
Total	200	78(39%)	21(10.5%)	99(49.5%)	200	16(8%)	0	16(8%)	0.001

T- Trimester, *n-number of cases or controls,*
SCH-Sub clinical hypothyroidism, *OH- Overt hypothyroidism*

Table 5.Trimester wise prevalence of Overt and Subclinical Hypothyroidism according to Indian Reference Range(IRR)

T	Cases				Controls				
	n	SCH	OH	total	n	SCH	OH	total	P Value
I	41	3(7.3%)	3(7.3%)	6(14.6%)	41	0	0	0	0.01
II	40	2(5%)	1(2.5%)	3(7.5%)	40	0	0	0	0.03
III	119	7(5.8%)	10(8.4%)	17(14.2%)	119	0	0	0	0.001
Total	200	12(6%)	14(7%)	26(13%)	200	0	0	0	0.001

T- Trimester, *n-number of cases or controls,*
SCH-Sub clinical hypothyroidism, *OH- Overt hypothyroidism*

On the whole it has been observed that the number of women with Hypothyroidism were more in cases when compared to controls considering both TES or IRR trimester specific cutoff values for pregnancy. The difference was statistically significant with P value 0.001 for TES criteria and 0.001 for IRR criteria.

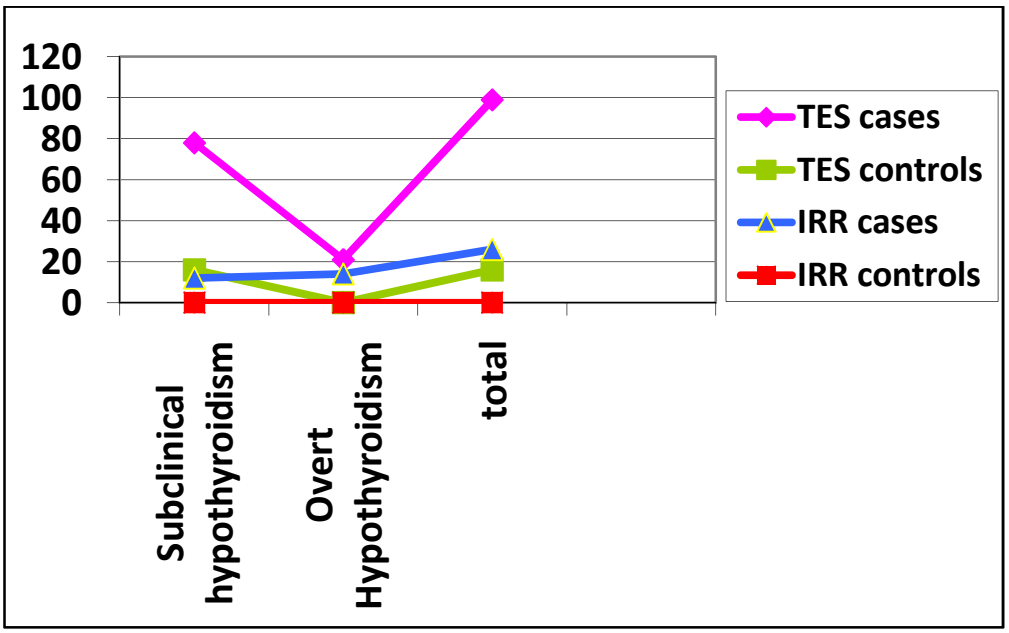
On the whole it has been observed that the number of women with Hypothyroidism were more in cases when compared to controls considering both TES or IRR trimester specific cutoff values for pregnancy. The difference was statistically significant with P value 0.001 for TES criteria and 0.001 for IRR criteria.

Prevalence of Subclinical hypothyroidism in cases was 38% according to TES criteria and 6% according to IRR criteria. Prevalence of Overt hypothyroidism in cases according to TES is 10.5% and 7% according to IRR. This difference was because in S.TSH value more than 2.5mIU/L in 1^{st} trimester and 3.IU/L in 2^{nd} and 3^{rd} trimesters is considered hypothyroidism as per TES criteria where as S.TSH more than 5 mIU/L in 1^{st} trimester 5.7mIU/L in 2^{nd} and 3^{rd} is considered hypothyroidism as per IRR criteria so the number of women diagnosed as hypothyroid according to IRR are less than that of TES criteria.

Prevalence of Overt hypothyroidism in cases according to TES is 10.5% and IRR is 7%.

In control group according to TES the prevalence of Sub clinical hypothyroidism is 8% and none of the controls were detected to be Overt hypothyroid and according to IRR there were no Subclinical or Over Hypothyroid women detected. This difference in prevalence is also due to lower and higher S.TSH cutoff values for diagnosis of hypothyroidism in TES and IRR criteria respectively.

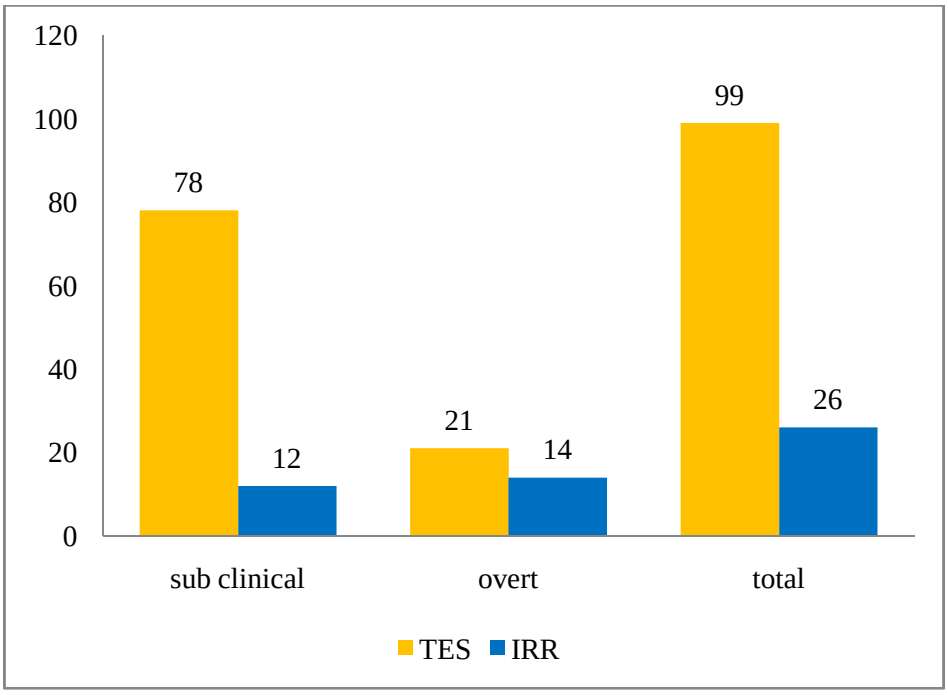
Graph3: Prevalence of hypothyroidism in cases and controls according to TES and IRR cutoff values



As discussed previously it is clearly seen here than the Subclinical hypothyroid cases are 78 and Overt hypothyroid cases 21 according to TES and 12 and 14 according to IRR and the number of hypothyroid women detected are higher according to TES criteria rather than IRR criteria. This is indicated by pink and blue lines.

In controls 16 women were detected to be Subclinical hypothyroid according to TES and there were no women with Subclinical hypothyroidism in control group according to IRR criteria and none were detected with Overt hypothyroidism in controls group according to both TES & IRR criteria. This is indicated by green and red lines.

Graph 4:Total Prevalence of hypothyroidism in cases according to TES and IRR cutoff values



Graph 5: Total Prevalence of hypothyroidism in controls according to TES and IRR cutoff values

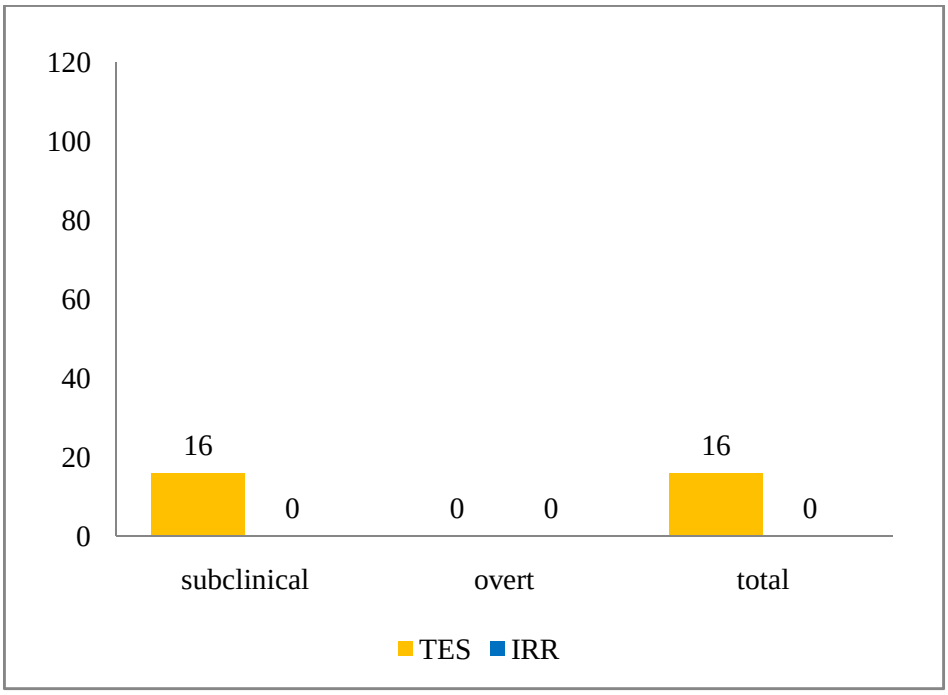
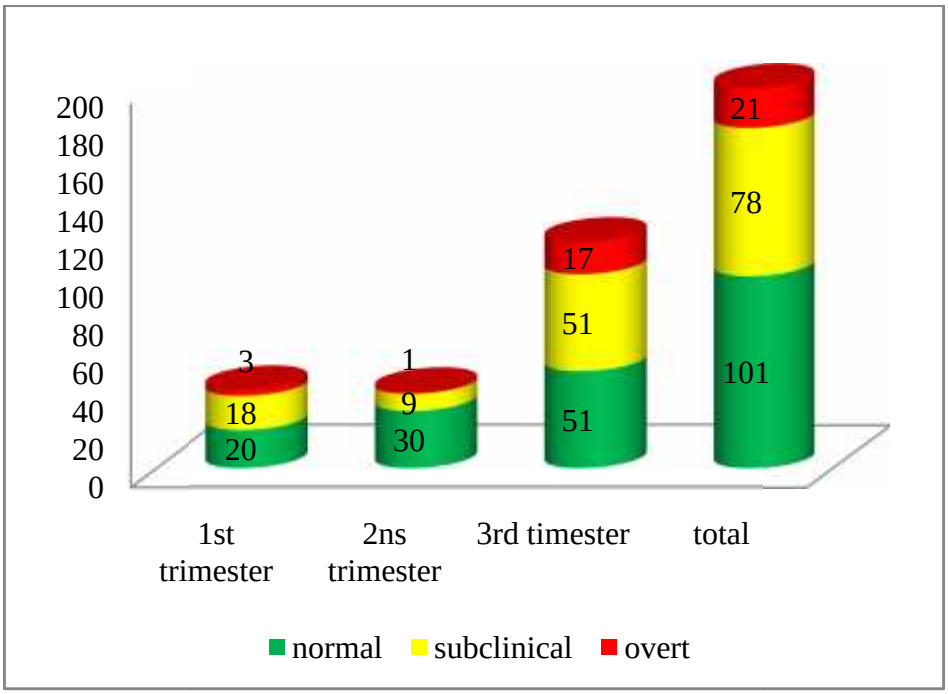


Table 6: Trimester wise Prevalence of hypothyroidism in cases(TES)

TRIMESTER	Cases			
	n	Subclinical hypothyroidism	Overt Hypothyroidism	total
I	41	18(43%)	3(7.3%)	21(51.2%)
II	40	9(22.5%)	1(2.5%)	10(25%)
III	119	51(42.8%)	17(14.2%)	68(57.1%)
Total	200	78(39%)	21(10.5%)	99(49.5%)

Graph 6: Trimester wise prevalence of hypothyroidism in Cases (TES)



Among 200 cases 41 of them were recruited in 1st trimester and most of them had spontaneous abortion(38) as adverse pregnancy outcome and when analyzed according to Thyroid Endocrine Scociety criteria for 1st trimester cutoff 18 were

detected to be Subclinical hypothyroid cases and 3 of them were detected to be Overt hypothyroid and a total of 21 cases were hypothyroid which accounts to 51.2%.

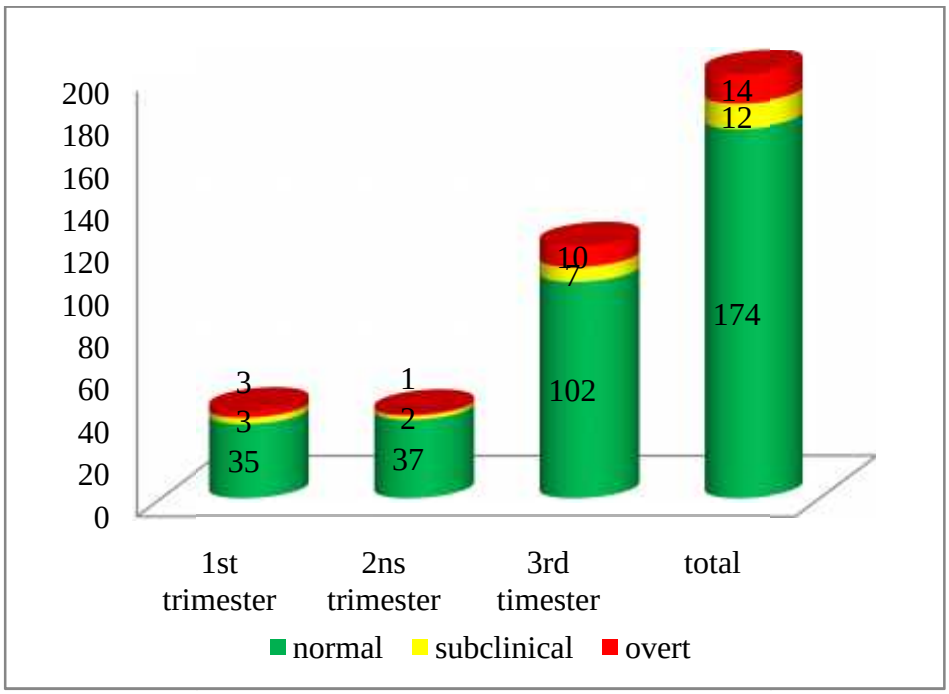
And among 40 cases in 2nd trimester 9 were Subclinical hypothyroid and only 1 was overt hypothyroid and a total of 10 women were hypothyroid which accounts for 25%.

And the highest women were recruited in 3rd trimester, so among 119 cases 51 are Subclinical hypothyroid and 21 were overt hypothyroid and a total of 68 women were hypothyroid in cases and accounts for 57.1%.

Table 7: Trimester wise prevalence of hypothyroidism in cases(IRR)

TRIMESTER	n	Cases		
		Subclinical Hypothyroid	Overt Hypothyroid	total
I	41	3(7.3%)	3(7.3%)	6(14.6%)
II	40	2(5%)	1(2.5%)	3(7.5%)
III	119	7(5.8%)	10(8.4%)	17(14.2%)
Total	200	12(6%)	14(7%)	26(13%)

Graph 7: Trimester wise prevalence of hypothyroidism in Cases (IRR)



Among 200 cases 41 of them were recruited in 1st trimester and when analyzed according to Pregnancy specific Indian reference Range (IRR) values for 1st trimester 3 were detected to be Subclinical hypothyroid cases and 3 of them were

detected to be Overt hypothyroid and a total of 6 cases were hypothyroid which accounts to 14.6%.

And among 40 cases in 2nd trimester 2 were Subclinical hypothyroid and only 1 was overt hypothyroid and a total of 3 women were hypothyroid which accounts for 7.5%.

The highest women were recruited in 3rd trimester, so among 119 cases 7 were Subclinical hypothyroid and 10 were overt hypothyroid and a total of 17 women were hypothyroid in cases and accounts for 14.2%.

Table:8 Analysis of adverse pregnancy outcomes in cases according to TES cutoff values and strength of association between each adverse pregnancy outcome and hypothyroidism

COMPLICATION	n	Hypothyroid (Subclinical and Overt)	percentage	Odds Ratio	95%confidence Interval
Spontaneous abortion	38	15	38%	7.5	3.28-17.5
Hyperemesis	3	0	0%	0	0
Pre eclampsia	91	44	48.5%	10.7	5.58-20.7
Eclampsia	6	2	33%	5.7	0.97-33.8
Abruptio Placenta	28	12	42.8%	8.6	3.48-21.34
GDM	32	12	37.5%	6.9	2.86-16.62
IUGR	71	28	39.4%	7.4	3.72-15.05
IUD	26	9	34.6%	6.0	2.3-15.8
Spontaneous preterm	21	3	14.2%	1.9	0.5-7.2

In this study it has been obsereved that Preclampsia has highest association with Hypothyroidism among all adverse pregnancy outcomes considered in the study with odd's ratio of 10.7.which is followed by Abruptio placenta with odds ratio of 8.6 and then by Spontaneous abortion and IUGR with odds ratio of 7.5 and 7.4 respectively and least association was observed with Spontaneous preterm and hypothyroidism with Odd's ratio of 1.9.

Table:9 Strength of association regarding prevalence of Hypothyroidism in cases and controls according to TES

TRIMESTER	Odd's Ratio	95% Confidence interval
I	6.12	2.12-17.68
II	6.33	1.28-31.11
III	18.5	8.27-41.3
Total	11.27	6.3-20.15

In this study in was observed that the association of hypothyroidism was 11.27 times more in cases in comparision with the controls.

DISCUSSION

Universal screening *Versus* case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy and pregnancy specific cutoff levels versus universal cut off for the treatment of thyroid dysfunction have been much debated topics of discussion. Currently, no consensus has been reached on the universal screening for thyroid function for pregnant women.

ACOG recommended thyroid function screening during pregnancy should be limited to women with symptoms of thyroid disease and those with past or family history of thyroid disease or other medical conditions associated with it .However such conventional screening may be insufficient because in most of the pregnant women that have thyroid dysfunction symptoms may be masked and even Subclinical hypothyroidism has adverse effect on pregnancy outcome.

Therefore this case control study was conducted to find association of hypothyroidism in pregnant women with adverse pregnancy outcome compared to pregnant women with normal pregnancy outcome .The present study was done at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, KLE University's teaching hospital attached to Jawaharlal Nehru Medical College Belgaum. A total of 400 pregnant women were recruited for the study and divided in to cases and controls after fulfilling the criteria of the group and were screened for hypothyroidism.

The prevalence of Subclinical hypothyroidism in this study in cases according to TES criteria is 39% and according to IRR criteria it is 6% and in control group Subclinical hypothyroidism 8% according to TES and no controls were found to have subclinical hypothyroidism according to IRR criteria. The Prevalence of

Hypothyroidism in cases was significantly high when compared to controls according to both TES or IRR criteria as trimester specific cutoff values for pregnancy. The number is statistically significant with P value 0.001 according to TES criteria and 0.001 according to IRR criteria.

This difference was because according to TES criteria S.TSH value more than 2.5mIU/L in 1st trimester and 3IU/L in 2nd and 3rd trimesters is considered hypothyroidism and according to IRR criteria S.TSH more than 5 mIU/L in 1st trimester 5.7mIU/L in 2nd and 3rd is considered hypothyroidism so the number of women diagnosed to have hypothyroidism, according to IRR criteria are less than that of TES criteria. However the prevalence of hypothyroidism was statistically significant in cases as compared to controls according to both TES and IRR criteria.

Prevalence of Overt hypothyroidism in cases according to TES criteria was 10.5% and IRR criteria was 7%. There is no much difference in the prevalence of overt hypothyroidism according to TES and IRR criteria as the serum TSH (≥10 mIU/L) cutoff value for diagnosis of overt hypothyroidism is same in both the criteria. In the present study most of the overt hypothyroidism women had a S.TSH value of ≥ 10mIU/L.

In a study by Altomare M et al(2013) studies 951 women at different gestational ages of pregnancy in Italy reported that prevalence of hypothyroidism was 12.3% .[83]

The prevalence of both OH and SCH was higher in the high-risk group(family history and bad obstetric history) than in the low-risk group, but 17.9% of women with hypothyroidism were of low-risk group. In this study the criteria for high risk

group was women with family history of thyroid dysfunction and bad obstetric history, which was different from current study where adverse pregnancy outcomes were exclusively studied and family history of thyroid dysfunction was an exclusion criteria hence the prevalence is not concurring.[83]

Brian M. Casey et al (2005) retrospectively studied 25,756 women about subclinical hypothyroidism and found that pregnancies in women with subclinical hypothyroidism were 3 times more likely to be complicated by placental abruption. Preterm birth, that is delivery at or before 34 weeks of gestation was almost 2-fold higher in women with subclinical hypothyroidism.

The overall prevalence of Subclinical hypothyroidism in pregnancy was 2.3% which is definitely less than that of the present study, as the cutoff value of S.TSH taken for diagnosing hypothyroidism was high

(S.TSH >6mIU/L) hence the number of cases detected to have hypothyroidism are less.[84]

According to the Indian studies, there was a study done by Vimal Nambiar (2011) with a cohort comprised of 483 consecutive pregnant women in the first trimester attending the antenatal clinic in Mumbai, India according to this study the prevalence of hypothyroidism was 4.8% (n = 24) which is definitely high compared to western literature but low compared to the present study as the S.TSH cutoffs values taken for this study were high that is 6mIU/L.[85]

This high S.TSH cutoff value of 6mIU/L was probably taken because of ethnic factors which are responsible for slightly higher prevalence of hypothyroidism in the Asian population.

Similarly another study was done by Dinesh K Dhanwal et al (2013) in New Delhi, which prospectively studied 1000 pregnant women in 1st trimester and found that the prevalence of hypothyroidism was 14.3% with S.TSH cutoff values of more than 4.5mIU/L to diagnose hypothyroidism.[86]

The overall prevalence in the present study is 28% which is almost double as compared to other studies as the S.TSH cutoff values taken to diagnose hypothyroidism in pregnancy and trimester specific more over all the three trimesters were included in the present study but the prevalence of hypothyroidism according to IRR criteria in the 1st trimester with

S.TSH ≥ 5mIU/L in present study(14.6%) is almost comparable to the study by Dinesh K Dhanwal et al (14.3%).

When we analyzed the association of hypothyroidism and individual adverse pregnancy outcome, it was observed that prevalence of hypothyroidism in Spontaneous Abortion 38%, Pre eclampsia 48.5% ,Eclampsia 33%,Abruption 42.8% ,GDM 37.5%, IUGR 39.4%, IUD 34.6%, Spontaneous preterm 14.2% according to TES criteria.

In another study by Msanao Ohashi et al(2013) in Japan where they retrospectively reviewed the medical charts of 392 pregnant women with obstetrical or medical complications and were divided according to clinical presentation, symptoms of thyroid disease and those with a personal history of thyroid disease, intrauterine growth restriction, diabetes mellitus ,hypertension ,intrauterine fetal death and placental abruption and found that the overall prevalence of hypothyroidism was 24.7% and in our study it is high that is 49.5% as they have taken S.TSH levels

greater than 4.5mIU/L and we have taken trimester specific S.TSH cutoff values(third trimester ≥3mIU/L)as per TES criteria. [87]

The prevalence of hypothyroidism in IUGR was 25% and according to our study by taking TES criteria was 39%, in there study the prevalence of hypothyroidism in diabetes group is 30%and In our study 37% were diagnosed to be hypothyroid by TES criteria which is almost concurring with the study done by Msanao Ohashi et al.

The prevalence of hypothyroidism in hypertension group was 27% in there study and in our study the prevalence of hypothyroidism in preeclampsia was 48.5% and which is almost twice that of the prevalence in this study and in our study it has been observed that Preclampsia has highest association with Hypothyroidism among all adverse pregnancy outcomes considered in the study with odd's ratio of 10.7.

In this study the prevalence of hypothyroidism in IUFD group was 12%and in our study the prevalence was 34% which is high compared to that of the study by Msanao Ohashi et al. and the prevalence of abruption placentae in Msanao et al's study was 7% and in our study it was 42% with 2nd highest association with hypothyroidism with odds ratio of 8.6. The difference in prevalence was basically because they have taken S.TSH levels greater than 4.5mIU/L and we have taken 3mIU/L for 2nd and 3rd trimester according to recommendations by TES and the ethnic factors are also responsible for the variation As in our study population where the prevalence of hypothyroidism is slightly higher in the Asian population especially Indian and Indian sub continental population.

Allan W C et al (2000) from Massachusetts, USA have done a cohort study in pregnant women and found the prevalence of hypothyroidism to be 2.2% which is not concurring with this study as they considered only the pregnant women of TSH levels more than 6mU/l as hypothyroid unlike our study where we considered more than 2.5mU/l in 1st trimester and 3mU/l in 2nd and 3rd trimester to be hypothyroid, so the number of cases detected to be hypothyroid are more compared to that of the study by Allan WC et al and they found that the rate of fetal death was significantly higher in those pregnancies (3.8%) than in the women with TSH less than 6 mU/l (0.9%, odds ratio 4.4, 95% confidence interval 1.9–9.5) [88] Other pregnancy complications did not occur more frequently.

Unlike our study, where we found there is greater association of hypothyroidism with Preeclampsia(Odd's ratio 10.7) which was not studied by Allan WC et al and association with IUD in our study was with Odd's ratio 6.0 was almost consistent with this study. [88]

Another study in USA by Männistö T et al (2013) retrospectively analyzed singleton pregnancies and found hypothyroidism was associated with increased odds of preeclampsia (OR = 1.47), superimposed preeclampsia (OR = 2.25) which is less than that of our study where the Odds ratio with preeclampsia was 10.7.

In their study association of hypothyroidism with gestational diabetes was (OR = 1.57)and the association in our study is with Odd's ratio of 6.9 which is definitely higher than in their study

When the association was studied with preterm birth they found (OR = 1.34) and in our study the association of hypothyroidism and preterm birth was found to be

(Odd's ratio is 1.6) which is similar to that of this study but when compared with other adverse pregnancy outcomes in our study preterm births had the least association with hypothyroidism.

The association of placental abruption with this study was (OR = 2.89) which is less than that of our study where the Odd's ratio for placental abruption in our study was 8.6.[89]

Coming to the studies which have Individually analyzed single adverse pregnancy outcome in hypothyroidism as Tudela CM et al (2012) found 4.9% of women had hypothyroidism and diabetes where as in our study we found 37.5% of pregnant women were hypothyroid and gestational diabetes mellitus which is higher than that of this study[90].

Breathnach FM(2013)in Ireland reported that Placental abruption was observed more commonly in the setting of either SCH or isolated maternal hypothyroxinaemia when compared with euthyroid controls (P = 0.02 and 0.04, respectively) these results were concurring with the results of our study where we found a strong association of hypothyroidism and placental abruption with Odds ratio 8.6.[91]

Most of the above studies have taken the Sr.TSH value more that 4.5mIU/l or 6mIU/l so have got the prevalence of hypothyroidism less than that of the our study. But as per the recommendations of Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease

During Pregnancy and Postpartum 2011 suggest that that Sr.TSH more than 2.5mIU/l in 1st trimester and 3mIU/l in 2nd and 3rd trimester should be considered

Hypothyroid and should be treated. So may be until the controversy regarding the universal screening settles thyroid screening should be offered to all the women with previous or present bad obstetric history along with the women with family history of hypothyroidism or related medical conditions. It is worthwhile screening for hypothyroidism in such women which would lead to early diagnosis and better obstetric outcome.

CONCLUSION

In the present study it was observed that the prevalence of hypothyroidism is significantly higher in cases when compared to controls according to trimester specific TES criteria (p=0.001) and IRR criteria (p=0.0001) values as cutoffs and the Odd's ratio of 11.27 and 95% confidence interval between cases and controls (6.3 & 20.15).

More number of hypothyroid women can be detected by using the trimester specific thyroid endocrine society cutoff values than to trimester specific Indian reference range cutoff values for pregnancy as the cutoff value of S.TSH is lower for TES criteria. So for a clinical set up it is recommended to follow TES criteria for the screening of hypothyroidism in pregnancy.

When individual complications of pregnancy and association with hypothyroidism were considered it was observed that 48.5%(TES) of Preeclampsia cases were found to be hypothyroid and with the highest odds ratio of 10.7(95% confidence interval between 5.58-20.7) Increased association was observed for Abruption(OD-8.6 95% CI-3.48-21.34), spontaneous abortions(OD-7.5 95%CI-3.28-17.5), Intra uterine growth retardation(OD-7.4 95%CI-3.72-15.05) gestational diabetes mellitus(OD-6.9 95%CI-2.86-16.6), and Intra uterine death(OD-6.0 95%CI-2.3-15.8) and the least association was observed with spontaneous preterm births (OD-1.9 95%CI-0.5-7.2)

Hence Until the controversy regarding Universal screening versus screening for targeted high risk pregnant women settles, it is advisable to offer screening for women with present adverse pregnancy outcome. It is worthwhile screening these

women as hypothyroidism can be detected especially Subclinical hypothyroidism early and treated by LT4 replacement would probably reduce adverse pregnancy outcomes associated with hypothyroidism.

SUMMARY

The present study was undertaken to evaluate the association of hypothyroidism in pregnant women with adverse pregnancy outcome and compare it with pregnant women with normal pregnancy outcome and also to compare the association of Hypothyroidism using Thyroid Endocrine Society (TES) and Indian reference range (IRR) pregnancy specific cut off values.

This one year case control study was conducted in the Department of Obstetrics and Gynecology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, KLE University's teaching hospital attached to Jawaharlal Nehru Medical College Belgaum during the period of January 2012 to December 2012. A total of 400 pregnant women were recruited for the study and divided in to cases and controls after fulfilling the criteria of the group and were screened for hypothyroidism based on S.TSH, FT4 and FT3 values in both cases and controls and were diagnosed as Euthyroid, Subclinical hypothyroid and Overt hypothyroid and results were analyzed .

In the present study the prevalence of Subclinical hypothyroidism in cases according to trimester specific TES criteria was 39% and 6% was noted in IRR criteria. In control group prevalence of Subclinical hypothyroidism was 8 % according to TES criteria and none of the controls were found to have subclinical hypothyroidism according to IRR criteria. This difference in prevalence was because of the lower trimester specific S.TSH cutoff values for diagnosis of hypothyroidism as per TES criteria as compared to IRR criteria. However the Prevalence of Hypothyroidism in cases was significantly high when compared to controls taking

both TES and IRR trimester specific cutoff values for pregnancy. The number is statistically significant with P value 0.001 according to TES criteria and 0.001 according to IRR criteria. The Odds ratio for strength of association was 11.27 with 95% confidence interval 6.3 & 20.15 between cases and controls.

Prevalence of Overt hypothyroidism in cases according to TES criteria was 10.5% and IRR criteria was 7% here there was no much difference in the prevalence of overt hypothyroidism as the S.TSH cutoff value (≥10mIU/L) for diagnosis of overt hypothyroidism is same in both TES and IRR criteria .In the present study most of the Overt hypothyroid women had S.TSH value of >10mIU/L.

More number of hypothyroid women can be detected by using the trimester specific TES criteria cutoff value than to trimester specific IRR that's the Indian reference values as the S.TSH cutoff value is lower in TES criteria as compared to IRR criteria. So for a clinical set up it is recommended to follow TES criteria for the diagnosis of hypothyroidism in pregnancy.

When individual complications of pregnancy and association with hypothyroidism were considered, it was analyzed that 48.5%(TES) of Preeclampsia cases were found to be hypothyroid and with the highest odds ratio of 10.7(95% confidence interval between 5.58-20.7) Increased association was observed for Abruption(OD-8.6 95% CI-3.48-21.34), spontaneous abortions(OD-7.5 95%CI-3.28-17.5), Intra uterine growth retardation(OD-7.4 95%CI-3.72-15.05) gestational diabetes mellitus(OD-6.9 95%CI-2.86-16.6), and Intra uterine death(OD-6.0 95%CI-2.3-15.8) and the least association was observed with spontaneous preterm births (OD-1.9 95%CI-0.5-7.2)

Hence Until the controversy regarding Universal screening versus screening for targeted high risk pregnant women settles, it is advisable to offer screening for women with present adverse pregnancy outcome. It is worthwhile screening these women as hypothyroidism can be detected especially Subclinical hypothyroidism early and treated by LT4 replacement would probably reduce adverse pregnancy outcomes associated with hypothyroidism.

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ANNEXURE-I

INFORMED CONSENT FORM FOR PARTICIPATION IN THE RESEARCH STUDY

TITLE: A CASE CONTROL STUDY TO EVALUATE THE CORRELATION OF HYPOTHYROIDISM IN PREGNANT WOMEN WITH ADVERSE PREGNANCY OUTCOME COMPARED TO PREGNANT WOMEN WITH NORMAL PREGNANCY OUTCOME

Objective/purpose of the study: We request you to participate in a study conducted by Dr. _____, Postgraduate in the department of Obstetrics and Gynaecology KLE University's teaching Hospital Belgaum, under the direct supervision and guidance of Dr. _____, Professor of Obstetrics and Gynaecology KLE University's Teaching Hospital. The study is an attempt evaluates the correlation of hypothyroidism in pregnant women with adverse pregnancy complications and compares it with normal pregnant women. Patient who fulfil the eligibility criteria will be included in the study. Your participation in the study will help us to derive a conclusion which will be beneficial to the larger population.

Procedure: You will be asked to provide some personal identification information and obstetric and past history relevant to the study. You will be subjected to investigations for TSH, FreeT3 and Free T4.

Risk and benefits: There is no additional risk involved in the procedure. There will be no financial incentives for being a part of the study.

Your participation in the study is purely voluntary. Your decision will not affect your relationship with the institute or in standard of care provided to you.

Privacy and confidentiality: Every effort will be made to protect the confidentiality of the information provided by you. Results of the study may be published for scientific purposes, but your name will not be used.

If you have any questions about the study you can contact Dr. _____ Professor, Department of Obstetrics and Gynaecology. In case you need any further information regarding your right as a study participant, You may please contact Dr. _____, Chairman of JNMC Institutional Ethical Committee.

I, volunteer and consent to participate in the study. I have read the consent or has been read to me. The study has been fully explained to me and I was given an opportunity to ask questions and receive answers.

Signature/thumb impression of participant:

Signature/thumb impression of witness:

Signature of investigator:

Date:

ANNEXURE II

DATA COLLECTION INSTRUMENT

PROFORMA

A CASE CONTROL STUDY TO EVALUATE THE CORRELATION OF HYPOTHYROIDISM IN PREGNANT WOMEN WITH ADVERSE PREGNANCY OUTCOME COMPARED TO PREGNANT WOMEN WITH NORMAL PREGNANCY OUTCOME

Sl. No. Date:

OP/IP No. Unit:

Patients Name

Age

Address

Contact No.:

Obstetric history

G: P: L: A: D:

Married life

History of infertility Yes / No

Past/Present history of thyroid disease: Yes/No

Family history of thyroid disease : Yes/No

Menstrual history

LMP

EDD

Period of Gestation:

Examination findings:

GPE: Height(cms): Weight(Kgs): BMI: Pulse:

BP:

Pallor ☐ Pedal edema ☐ Icterus ☐ Thyroid swelling ☐

CVS:

RS:

P/A: Fundal height: Presentation: FHS:

P/S:

P/V:

ADVERSE PREGNANCY COMPLICATIONS

	Past Pregnancy		Present pregnancy	
	YES	NO	YES	NO
Spontaneous Abortion	☐	☐	☐	☐
Hyperemesis Gravidarum	☐	☐	☐	☐
Spontaneous Preterm labour	☐	☐	☐	☐
G. HTN/Preeclampsia	☐	☐	☐	☐
Eclampsia	☐	☐	☐	☐
Abruptio Placenta	☐	☐	☐	☐
Gestational Diabetes	☐	☐	☐	☐
IUGR	☐	☐	☐	☐
IUFD	☐	☐	☐	☐

CASE ☐ CONTROL ☐

Thyroid function tests

PERIOD OF GESTATION	TSH	FREE T3	FREE T4
1ST TRIMISTER			
2ND TRIMISTER			
3RD TRIMISTER			

ANNEXURE III – KEY TO MASTER CHART

BP	- Blood Pressure
BMI	- Body Mass Index
CM	- CentiMeter
EDD	- Expected Date of Delivery
FT3	- Free Triiodothyronine
FT4	- Free Tetraiodothyronine/Thyroxine
gm	- Grams
IUD	- Intra Uterine Death
IUGR	- Intrauterine growth retardation
Kg	- Kilogram
LMP	- Last Menstrual Period
TSH	- Thyroid Stimulating Hormone

ANNEXURE IV – ETHICAL CLEARANCE LETTER

K.L.E.SOCIETY'S
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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Ref: MDC/PG/ ೧೫೨ **Date: 21/10/2011**

To,
Dr. S.L.Avanti
Postgraduate Student,
Department of OBG,
J.N.Medical College,
BELGAUM.

Sub: Institutional Ethical Clearance for the study.

Dear Dr. S.L.Avanti,

With reference to the above, I wish to inform you that the research project "**A CASE CONTROL STUDY TO EVALUATE THE CORRELATION OF HYPOTHYROIDISM IN PREGNANT WOMEN WITH ADVERSE PREGNANCY OUTCOME COMPARED TO PREGNANT WOMEN WITH NORMAL PREGNANCY OUTCOME**", is Ethical and justifiable and has been cleared by the departmental Ethical Committee and College Dissertation and Research Committee.

(Dr. P.V. Patil),
Chairman
College Ethical Dissertation
And Research Committee,
J.N.Medical College, Belgaum.