HEARING EVALUATION IN INFANTS BORN TO HYPOTHYROID WOMEN

By

DR. INDU VARSHA G

Dissertation submitted to

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTRE, KOLAR

In partial fulfillment of the requirements for the degree of

MASTER OF SURGERY IN OTORHINOLARYNGOLOGY

Under the guidance of

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DEPARTMENT OF OTORHINOLARYNGOLOGY

SRI DEVARAJ URS MEDICAL COLLEGE

TAMAKA, KOLAR

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I hereby declare that this dissertation entitled **"HEARING EVALUATION IN INFANTS BORN TO HYPOTHYROID WOMEN"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. S.M AZEEM MOHIYUDDIN,** MBBS, MS, FICS, FACS, SEKHSARIA FELLOWSHIP IN HEAD AND NECK SURGERY, Professor and Head of the Department of Otorhinolaryngology and Head and Neck Surgery, Sri Devaraj Urs Medical College, Tamaka, Kolar in partial for the award of M.S degree in Otorhinolaryngology to be held in 2019. This dissertation has not been submitted in part or full to any other university or towards any other degree before this below mentioned date.

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Dr. INDU VARSHA G

LIST OF ABBREVIATIONS

OAE	⇨	Otoacoustic emissions
BERA	⇨	Brainstem Evoked Response Audiometry
TSH	⇨	Thyroid Stimulating Hormone
T3	⇨	Triiodothyronine
T4	⇨	Tetraiodothyronine
TRH	⇨	Thyrotrophin Releasing Hormone
HCG	⇨	Human Chorionic Gonadotropin
TPO	⇨	Thyroperoxidase Antibodies
TGAb	⇨	Anti-Thyroglobulin Antibodies
TSHRAb	⇨	ThyroidStimulating Hormone Receptor Antibodies
TSI	⇨	Thyroid Stimulating Immunoglobulin
TBII	⇨	Thyroid binding Inhibitory Immunoglobulin
UNHS	⇨	Universal Newborn Hearing Screening
NBS	⇨	Newborn Screening
TEOAE	⇨	Transient Evoked Otoacoustic Emissions
DPOAE	⇨	Distortion Product Otoacoustic Emissions
SNR	⇨	Signal-Noise Ratio

ABSTRACT

BACKGROUND:

Hypothyroidism is the most common endocrinological disorders in the reproductive age group in the developing countries. The prevalence is more for subclinical hypothyroidism and autoimmune thyroiditis. Studies have proved the transfer of Anti Thyroperoxidase antibodies through the placenta from the mother to the infants at the time of birth and causes adverse effects.

Maternal hypothyroidism can cause congenital hypothyroidism in infants. Hypothyroidism is known to cause sensorineural hearing loss because it can affect retrocochlear, cochlear and central auditory pathway especially in infants with congenital hypothyroidism. The early screening for hypothyroidism and hearing impairment in infants were insisted for early initiation of treatment and rehabilitation.

All the clinical studies were on hearing impairment in congenital hypothyroidism. There is lack of studies explaining the hearing outcome in infants born to women whose hypothyroidism is corrected during pregnancy and also in subclinical hypothyroidism.

We therefore performed an observational study to compare and document the hearing acquity in infants born to known hypothyroid (including subclinical hypothyroidism) women, treated for hypothyroidism during pregnancy and infants born to normal women and thereby facilitate early detection and correction of hearing and developmental delays in these infants in Kolar district.

OBJECTIVES:

1. To evaluate hearing by otoacoustic emissions and Brain Stem Evoked Response Audiometry in infants born to hypothyroid (including subclinical hypothyroidism) women and women treated for hypothyroidism during pregnancy and compare with hearing in infants born to euthyroid mothers.

2. Assess the hearing outcome in infants born to women who presented with hypothyroidism in early pregnancy and late pregnancy using otoacoustic emissions and Brain Stem Evoked Response Audiometry.

METHODS:

The study was done in 280 infants, 140 infants born to hypothyroid (including subclinical hypothyroidism) women or treated for hypothyroidism during pregnancy and 140 infants born to euthyroid women presenting to the Department of Obstetrics and Gynaecology and Department of Pediatrics in R L Jalappa Hospital &Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar from December 2016 to April 2018 using Otoacoustic Emissions and Brain stem Evoked Response Audiometry.

RESULTS:

The infants underwent audiological evaluation using Otoacoustic Emissions and Brain stem Evoked Response Audiometry at 1^{st} and 4^{th} month of life. All infants had normal TSH levels. Infants in the study group showed a lower birth weight when compared to the control group. The infants with family history of hypothyroidism had prolongation in the latency of replicability of wave V at 30dBnHL in BERA but was not clinically significant. Two infants in the study group showed delayed appearance of wave V on BERA. Infant who showed a delayed appearance of wave V at 6^{th} month of life was the

second twin with a birth weight of 1.2kg and born at 37weeks of gestation. The other infant showed wave V at 8th month of life. She was born to a lady with Hashimotos thyroiditis and was detected at the time of delivery. Around 50% of the infants in the study group showed a prolongation of the latencies of wave V replicability at 30dBnHL in BERA in 1st month of life when compared to control group. However by the 4th month of life it had got corrected. This delay was not statistically significant.

The results of our study showed that, infants born to women whose hypothyroidism was corrected during pregnancy had a delayed response (wave V) on sensitive hearing test like BERA. This could have been due to maternal hypothyroidism. However this minor delay on BERA was not statistically significant and it also got corrected by 4th month of life. This correction in hearing could be due to normal levels of thyroid hormones in infants after birth. The subtle deficiency in hearing was subclinical and got corrected because mothers' hypothyroidism was treated in time. Therefore correction of hypothyroidism in pregnant women is important. It is best done in early pregnancy.

CONCLUSION:

1. Hypothyroidism during pregnancy is common in Kolar region. However most of these cases are diagnosed and treated adequately before parturition.
2. Hypothyroidism affects the hearing in newborns born to women whose hypothyroidism is corrected during pregnancy and also in those who has a positive family history. However its effect on hearing of the infant was found to be minimal and transient when the circulating hormones in the infant are normal. Therefore this subtle deficiency in hearing during the first month of life was only subclinical.

3. It is important to screen the infants born to hypothyroid women for delay in developmental milestones as well as hearing impairment.
4. Otoacoustic emissions can only be a screening tool. BERA is more accurate and sensitive in diagnosing hearing impairment in newborns. Therefore BERA should be used to evaluate hearing in all infants born to women who had autoimmune thyroiditis, or whose hypothyroidism was corrected late in pregnancy. BERA must also be done in all infants with low birth weight, premature delivery and those found to have congenital or developmental anomalies.
5. Since this study was only a dissertation, studies with larger sample size would be required with estimation of Anti Thyroperoxidase antibodies soon after birth in infants born to hypothyroid women to document the risk of hearing impairment or the hazard ratio in these infants.

KEYWORDS:

Hypothyroidism, Newborn screening, Anti Thyroperoxidase antibodies, Hashimotos Thyroiditis, Otoacoustic Emissions, Brain stem Evoked Response Audiometry.

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INTRODUCTION

I. INTRODUCTION

Thyroid abnormalities are the most common endocrinological disorders, especially in the developing countries. In South India one among 8 women has Hypothyroidism with a prevalence of 11% among reproductive age groups which also includes subclinical hypothyroidism. Thyroid disease in pregnancy is one of the most important and common endocrinological disorder[1]. Overt maternal thyroid dysfunction and the presence of Thyroperoxidase antibodies in early gestation is an evidence of subclinical hypothyroidism, postpartum thyroid dysfunction and poor neonatal thyroid function. Thyroperoxidase antibodies have been documented to cross the placental barrier in literatures [2,3].

Thyroid gland produces hormones which regulate the body metabolism. Thyroxine is necessary for several body functions, including hearing. Thyroid disorders are often unnoticed because their presentations are often confused with other health related issues. Thyroid disorders can be either hyperthyroidism or hypothyroidism. Pregnancy influences the thyroid gland function[4].

Studies showed Thyroid hormones are essential for the inner as well as middle ear development. Both hyperthyroidism and hypothyroidism can be linked to hearing loss. Thyroxine helps in development of the cochlea. The risk of hearing impairment (sensorineural hearing loss) is high in infants with congenital hypothyroidism[5]. However only less number of studies has explored the prevalence of hearing loss in infants born to hypothyroid women and to women whose hypothyroidism was corrected during pregnancy with conflicting results.

In 1944 Ewing and Ewing first emphasized for the importance of newborn screening for hearing loss[6]. Over the next 25years there was awareness regarding newborn screening for hearing since congenital hearing loss is a frequent birth defect affecting 3 newborns per 1000 infants (white etal). The most commonly used audiologic screening is by Otoacoustic Emissions (OAE) and confirmed by Brain stem evoked response audiometry (BERA).Newborn screening and thyroxine therapy started at an early age can help the development of a child since children with even mild hearing loss may suffer from delayed speech, poor social and cognitive development and learning impairments[6].

We therefore performed an observational study to compare and document the hearing acquity in infants born to known hypothyroid (including subclinical hypothyroidism) women, treated for hypothyroidism during pregnancy and infants born to normal women and thereby facilitate early detection and correction of hearing and developmental delays in these infants in Kolar district.

OBJECTIVES OF THE STUDY

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1. To evaluate hearing by otoacoustic emissions and Brain Stem Evoked Response Audiometry in infants born to hypothyroid (including subclinical hypothyroidism) women and women treated for hypothyroidism during pregnancy and compare with hearing in infants born to euthyroid mothers.

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REVIEW OF LITERATURE

III. REVIEW OF LITERATURE

In South India the Hypothyroidism is common especially among women in their reproductive age, including subclinical hypothyroidism. Hypothyroidism detected can be either overt hypothyroidism or subclinical hypothyroidism[7]. Overt hypothyroidism is symptomatic thyroid deficiency and subclinical hypothyroidism shows no symptoms or only few expressed symptoms but with raised thyroid stimulating hormone. Normally thyroid function in pregnancy has a rise in Tetraiodothyronine level at 12weeks and a fall in hormone concentrations in the second half of the pregnancy[8].Women on Thyroxine for hypothyroidism, the dose usually being increased by up to 50% in pregnancy. Hashimoto's thyroiditis is the main cause for hypothyroidism with the presence of Antithyroperoxidase. It acts by inhibiting the Peroxidase enzyme and reduces the release of hormones by the thyroid gland[9].

Thyroid dysfunction and presence of antithyroperoxidase in a pregnant woman can cause thyroid agenesis or hormonal dysgenesis and can also affect the normal metabolism in an infant[9]. The literatures show a free passage of thyroperoxidase antibodies across the placental barrier from the mother to fetus at the time of childbirth and results in adverse fetal outcomes[10]. Thyroid hormones can affect the growth and development of various systems in the body including the auditory system. Sensorineural hearing loss is seen in infants born to hypothyroid women [11].

High risk infants have to be screened at an early age for hearing to prevent adverse outcomes. Otoacoustic emissions are an easy screening method for hearing evaluation for infants. It has a sound generator with a processing unit generating 75-80dB intensity. The

cochlea generates a response through the active movement of outer hair cells which is propogated to the outer ear and is collected by the microphone[12]. Hearing loss in infants detected by screening will be assessed and confirmed by Brain Stem Evoked Response Audiometry [BERA]. It is an objective method for documenting brain stem potentials. The recordings are in the form of peaks and troughs. The waves are labeled as I-VII. [13]

3.1. EPIDEMIOLOGY

Thyroid disease is a major health problem worldwide with significant effects on pregnancy and infants. Since the last 20years, the prevalence of suclinical thyroid disorders is reduced because of the implementation of awareness programs, adequate screening techniques and early treatment initiation. Iodine is needed for determining the thyroid imbalance. In iodine-deficient areas, multiple other risks factors like genetic and ethnic factors, sex, smoking history, alcohol consumption and autoimmune disorders can also affect the thyroid disease [14].

3.1.1. WORLDWIDE

The prevalence of Hypothyroidism is high worldwide and the most burden of the disease is seen in the UK and the lowest was among the Afro-Caribbean people. Many of the studies conducted worldwide for the prevalence of hypothyroidism, the largest study was conducted in the UK and found about 35 cases per 10,000 females and 6 cases per 10,000 males in a 20 year follow up period. The common causes for primary hypothyroidism are deficiency of iodine and Autoimmune Thyroiditis. Majority of the population is present in iodine deficient regions. In non- iodine deficient areas the prevalence of hypothyroidism

ranges from 1 to 2% and 7 to 8% in iodine-deficient areas[14]. Females are 5 times more commonly affected than the males. With the screening of hypothyroidism among pregnant women, the incidence is about 2%. Though routine screening is done during pregnancy there is no clear impact on the maternal and fetal effects. The subclinical hypothyroidism is about 4.6%, especially among Korean population. Above 60years of age, there is 20% chance of developing subclinical hypothyroidism in women[14].

3.1.2. INDIA

In India especially in the rural areas, the prevalence of the disease is more due to a lack of awareness about the disease, less availability of facilities and inadequate maternal and fetal screening programs. Studies showed about 42 million people in India are suffering from thyroid diseases. Women had 11.4% more prevalence than the males. There is high prevalence of hypothyroidism especially during pregnancy in India. Majority of the cases, 13.3%, have subclinical hypothyroidism in the first trimester of pregnancy. About 1 in 10 pregnant women had antithyroperoxidase or antithyroglobulin and there is a 16% chance for them to develop hypothyroidism. In case of subclinical hypothyroidism, there is 50% chance of the presence of antithyroperoxidase[15]. Maximum prevalence of hypothyroidism during pregnancy is present in Jammu and Kashmir about 39.0% and least was noticed in Karnataka that is 7.8%. The need for early detection by screening and its early treatment is necessary as India has more prevalence of hypothyroidism, especially in the rural parts[16].

3.2. ANATOMY AND EMBRYOLOGY OF THYROID

3.2.1. THYROID GLAND

The thyroid gland is an important endocrine organ which starts functioning from fetal life. It regulates the metabolism of each tissue and is essential for the normal function and for the physical and mental growth[17]. Hypothyroidism is a common disorder of the gland. The most common diagnostic test is the estimation of the level of Thyroid stimulating Hormone (TSH), which is 94% sensitive and is very effective in determining the thyroid disorders. Along with the TSH test, T3 and T4 testing are also done commonly in patients with thyroid diseases. The prevalence of hypothyroid disorder, among another endocrine disease, is high but the awareness among the people is lacking in our country [18].

3.2.2. ANATOMY OF THYROID

The thyroid gland derives its name from the Greek word *thyreos* meaning “shield”. The term thyroid for the gland was first named by Thomas Wharton in the 17th century. It weighs about 15 to 25g that is about 0.4% of the body mass [19].

The thyroid gland is a two lobed structure and is seen in front of the trachea. The two lobes are connected with a central isthmus. It is covered by a fibrous capsule which is continuous with the pretracheal fascia [19].

3.2.3. EMBRYOLOGY

Median analage of cells proliferate between the first and second brachial arches at the base of the tongue, which forms the Foramen Caecum. It forms the thyroid bud and a

diverticulum. It develops from the base of the tongue and lies anterior to the trachea [20]. The two lateral anlages or the 'ultimobranchial bodies' develop from the fourth pharyngeal pouch and fuse with the median anlage as the thyroid gland moves to the neck. The median analage forms the thyroid follicular cells and the lateral anlages form the parafollicular cells (C-cells) [21].

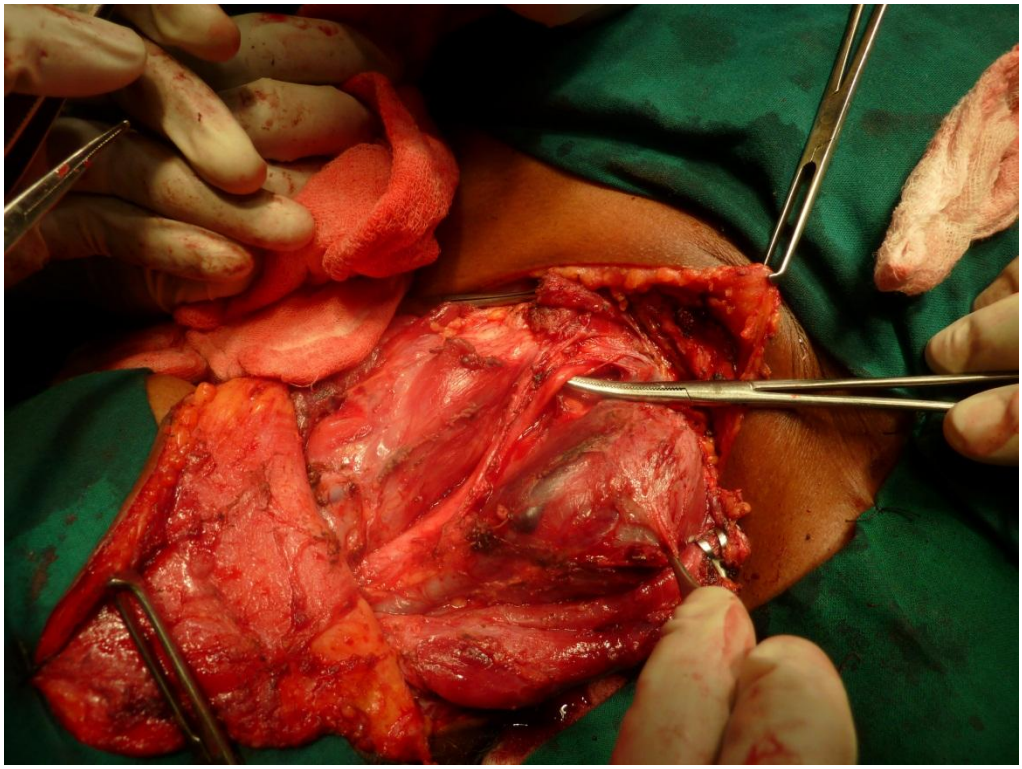


Figure 1: Showing the operative picture of the Thyroid gland

3.3 ANATOMY OF THE HUMAN AUDITORY SYSTEM

The auditory system can be of two parts: the peripheral and the central auditory system. The peripheral system includes the outer, middle and internal ear and the Eight nerve, while the central system has structures from the brainstem to the auditory cortex[22]

3.3.1. INNER EAR: The inner ear is responsible for hearing and balance. It has a bony and membranous labrynth. The vestibule, the semicircular canals and the cochlea is present in the bony labrynth[23].

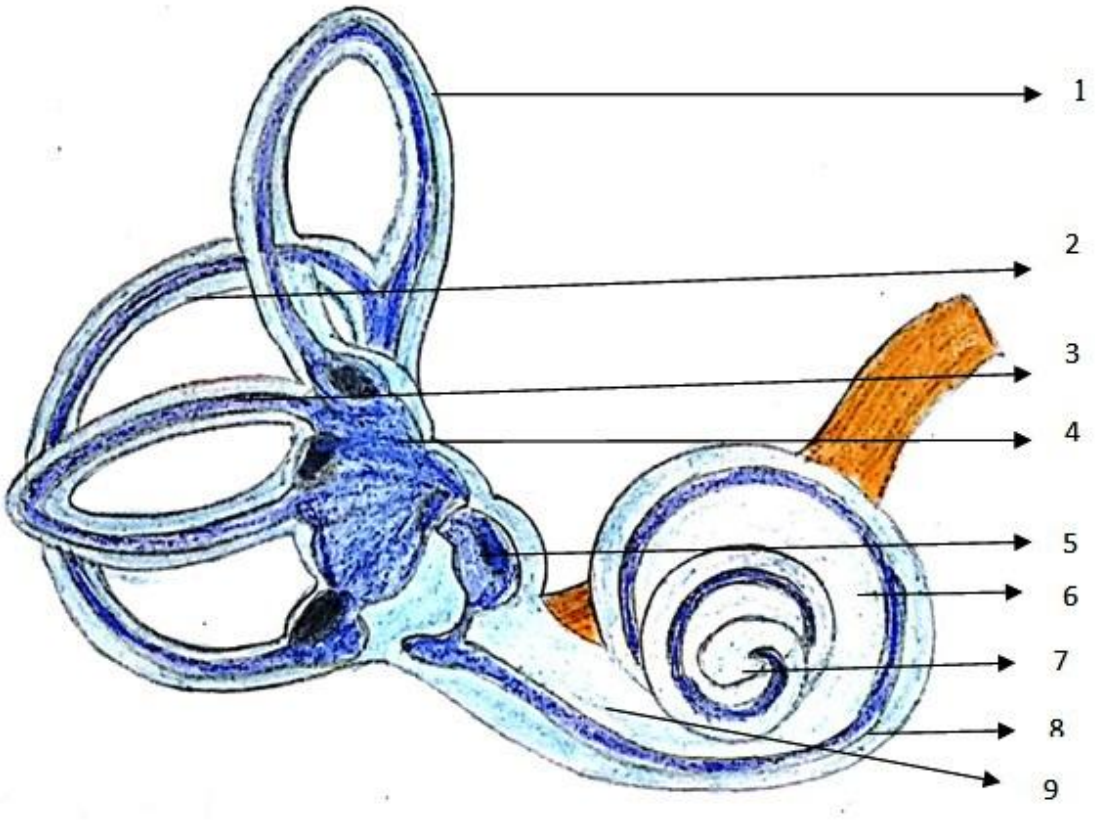


Figure 2: Showing the parts of inner ear. (1-Anterior Semicircular canal, 2-Posterior Semicircular canal, 3-Lateral Semicircular canal, 4-Utricle, 5-Saccule, 6-Cochlea, 7-Apex of Cochlea, 8- Cochlear duct, 9- Vestibule)

3.3.2. COCHLEA: The term cochlea is derived from the Latin word meaning snail. It is associated with hearing. It's a spiral structure where the sound wave is transformed into an electrical impulse. Human cochlea contains about two and a half turns[23]. The development of

cochlea occurs the end of first trimester of pregnancy and attains its full size by 19 weeks of gestsation.The cochlea is present within the cochlear duct in labrynth in the petrous part of the temporal bone. The development of the hair cells in the cochlea starts between the 10th and 12th weeks. The neurosensory part of the auditory system begins to develop after the 20th week. By the 24th week, the auditory system is structurally complete. The entire auditory system becomes active around 25th to 29th week and the ganglion cells of cochlear nucleus connect the inner hair cells to the brain stem[24].

The cochlea has three spiraling structures which include: the scala tympani , the scala vestibuli and the scala media. The scala tympani and the scala vestibuli contain perilymph and communicate through the helicotrema. The scala media contains endolymph. In the cochlea the waves propagate from the base to the apex due to inner ear fluids[23].

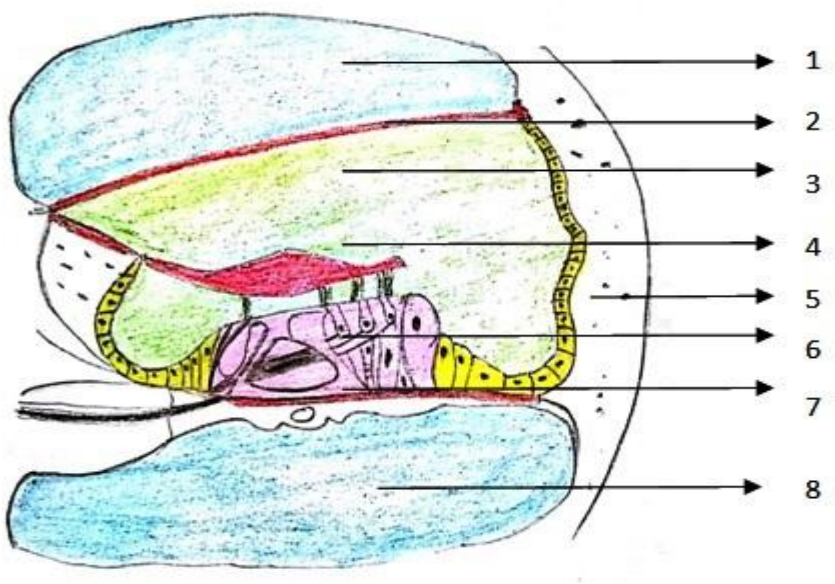


Figure 3: Showing the parts of the Cochlea. (1- Scala Vestibuli, 2-Resiner's Membrane, 3-Scala Media, 4-Tectorial Membrane, 5-Stria Vascularis, 6-Organ of Corti, 7-Basilar Membrane, 8-Scala Tympani).

The organ of Corti is a small structure present in the scala media on the basilar membrane that has hair cells and sensory receptors to the auditory nerve. The Tectorial membrane is above the hair cells in the Organ of Corti and helps them in producing the neural impulses of the sounds. [23]

Hair cells are receptors for hearing. They convert sound mechanical energy into electrical energy. There are inner and outer hair cells. Outer hair cells consist of three or four rows which modulate the actions of the inner hair cells. Inner hair cells are single row and are supplied by multiple afferent cochlear fibers[23].

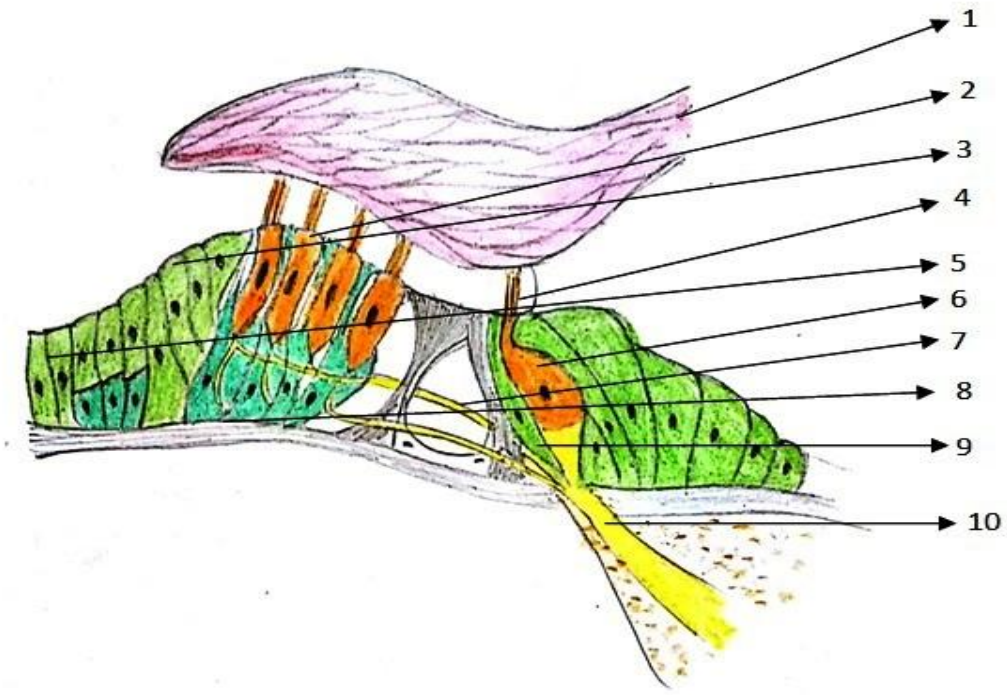


Figure 4: Showing the Organ of Corti. (1- Tectorial Membrane, 2-Outer Hair cell, 3-cells of Hensen, 4-Reticular Membrane, 5-Cells of Claudius, 6-Inner Hair cell, 7-Basilar Membrane, 8-Pillar Cells, 9-Nerve Fibres).

3.3.3. Auditory pathway: When a sound reaches the cochlea, it is converted into an electrical impulse and passes from the cochlea to the Auditory Cortex[25].

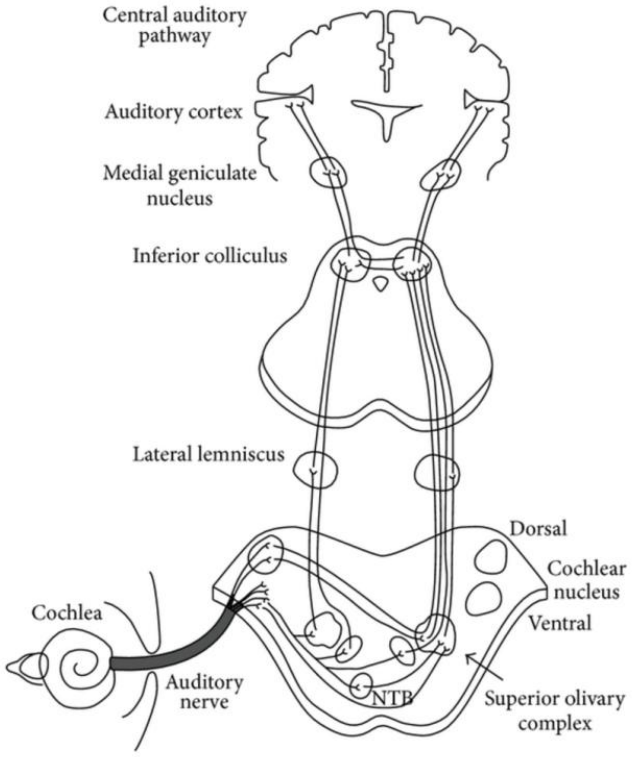


Figure 5: Showing the Auditory Pathway

3.4. PHYSIOLOGY OF THYROID GLAND

The endocrine system, the hormones maintain the homeostasis in an organism. The hormones from the thyroid are needed for the metabolism of every cell except adult brain, spleen, testes and uterus. Thyroid hormone stimulates the enzymes involved with the oxidation of carbohydrates, proteins and lipids thereby regulating the body's metabolic rate and heat production. Thyroid hormone increases the number of adrenergic receptors in blood

vessels and helps in regulation of blood pressure. It promotes tissue growth of skeleton, nervous and reproductive system[26.]

Thyroid hormones are not protein or cholesterol based. They contain iodine as an active component. It can be Thyroxine or Tetraiodothyronine (T4), with four iodine molecules and with three iodine molecules, Triiodothyronine (T3). The T4 :T3 in the body is 50:1.T3 is ten times more active than T4. T4 acts as the prohormone and acts in the Hypothalamus-pituitary negative feedback loop, while T3 has more physiological effects in the body[26].

3.4.1. THALAMOHYPOTHALAMO-PITUITARY AXIS

The formation, synthesis, storage and release of hormones from the thyroid are controlled by the Thalamohypothalamo-Pituitary axis.

The Thyrotrophin –releasing hormone (TRH) secreted from the Paraventricular nucleus of the Hypothalamus regulates the secretion of Thyrotropin or TSH. The TRH is taken through the axons and released into the hypo-physeal-portal blood circulation and is carried directly to the basophilic thyrotrophic cells of the Anterior Pituitary gland. The alpha-adrenergic agonists stimulate TSH secretion. It helps in iodide uptake by the thyroid gland and thereby helps in the release of thyroid hormones. The thyroid hormones, stomatostatin and dopamine can prevent the action of the thyrotroph[26].

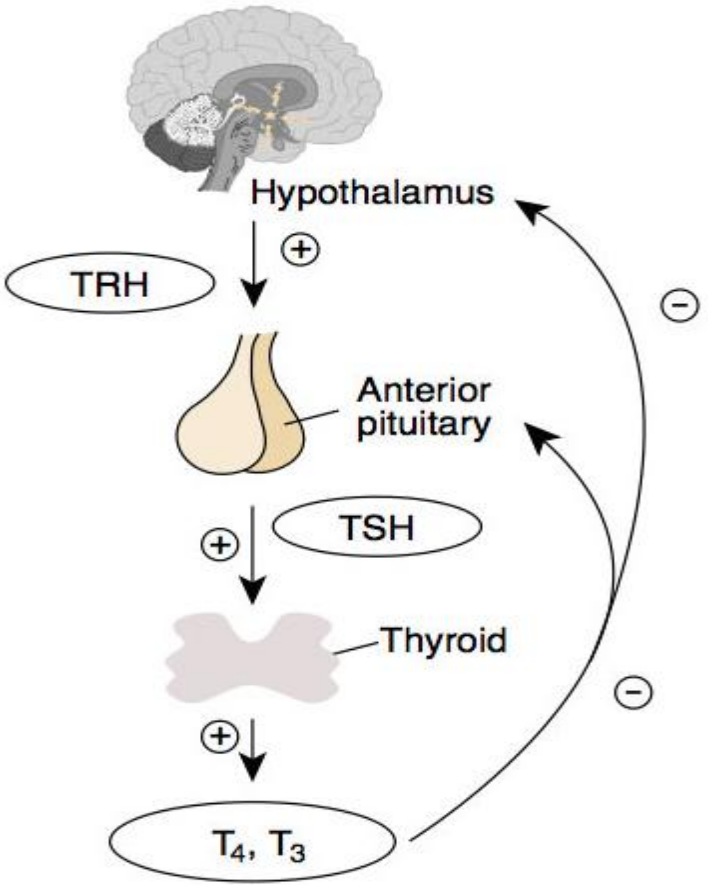


Figure 6: Showing the Hypothalamo-pituitary axis

3.4.2. HORMONES OF THE THYROID GLAND

The thyroid gland produces:

I. **Thyroxine/Tetraiodothyronine (T4):** It acts as inactive prohormone and forms 80% of the total thyroid hormones.

II. **Triiodothyronine (T3):** It is the active form and accounts for 20% of the total thyroid hormones.

III. **Calcitonin:** The thyroid gland also produces calcitonin from C-cells. Calcitonin helps in regulating calcium levels in the body [26].

3.4.3. PHYSIOLOGICAL EFFECTS OF THYROID HORMONES

It is mainly concerned with the body's metabolism[26].

TARGET TISSUES	EFFECTS	MECHANISMS
Heart	Chronotropic	Increases the number and affinity of adrenergic receptors
	Ionotropic	Enhances the responses to circulating catecholamines
Adipose tissue	Catabolic	Causes lipolysis
Bone	Developmental and metabolic	Promote growth and skeletal development and causes the bone to turn over
Muscle	Catabolic	Increases protein breakdown
Nervous system	Developmental	Causes normal brain development.
Gut	Metabolic	Increases the rate of carbohydrate absorption
Lipoprotein	Metabolic	Stimulates formation of LDL receptors
Others	Calorigenic	Increases the metabolic rate

Table 1: Showing the physiological effects of the thyroid hormones

3.4.4. HYPOTHYROIDISM

Hypothyroidism is a common endocrine disorder due to decreased secretion of thyroid hormones or reduced secretion of TRH or TSH. In Hypothyroidism, there is an

increased release of TSH by Pituitary resulting in thyroid hypertrophy and hyperplasia and causes release of more T3[27].

3.4.4.1. SUBCLINICAL HYPOTHYROIDISM

In Subclinical hypothyroidism patients are clinically asymptomatic with an increase in serum TSH and normal freeT4. It has a prevalence of 7-8 % in women and 2-4% in men and it rises with age to about 15% in women over 60years. Women with subclinical hypothyroidism show 60% presence of thyroid peroxidase antibodies. They can progress to overt hypothyroidism at the rate of around 2-5% per year Six monthly or Annual retesting can be done in patients who are asymptomatic with raised TSH(below 10mU/L) or with a low or negative titer of microsomal antibodies.[28]

3.4.4.2. OVERT HYPOTHYROIDISM

Overt hypothyroidism is characterized by an increased TSH and a decreased thyroid hormone levels.[28]

3.4.4.3 CAUSES OF HYPOTHYROIDISM

The causes of Hypothyroidism can be:

i. Autoimmune thyroiditis- common is Hashimoto thyroiditis and atrophic thyroiditis, develops antibodies against their own thyroid tissues.

ii. Iodine status of the patient.

iii. Iatrogenic: treatment with radioactive iodine (I-131) or External beam radiation to neck for head and neck cancers or post total thyroidectomy if replacement dose of Thyroxine is inadequate.

iv. Genetic causes- as in congenital hypothyroidism

v. Medications like amiodarone, lithium, monoclonal antibodies, sodium valproate, tyrosine kinase inhibitors and immune checkpoint inhibitors especially in patients who are genetic predisposition for autoimmune thyroid disorders.

vi. Post-partum thyroiditis or De Quervain syndrome

vii. Damage to the Pituitary gland due to tumour, radiation or surgery. It inhibits the release of TSH.[29]

3.4.5. MEASUREMENT OF THYROID HORMONE LEVELS

Measurement of T4 and TSH is significant. The levels of T3 show variations with ageing, weight loss and with the usage of drugs[26].

HORMONES	NEWBORN	ADULTS
T3	1-7ng/mL	0.7-2.0ng/mL
T4	11.8-22.6microg/dL	6.0-11.0microg/dL
TSH	1.0-39.0microIU/mL	0.5-5.0microIU/mL

Table 2: Showing measurement of the Thyroid gland

3.4.6. HYPOTHYROIDISM AND PREGNANCY

Thyroid disorders are the common in young women of child bearing age. Iodine deficiency is the predominant cause for it. The hormonal and immunologic variations during pregnancy and the post-partum period and the dependence of the fetus on maternal iodine and thyroid hormones can significantly influence the fetus. Overt hypothyroidism and thyrotoxicosis can result in abortions, fetal demise, preterm delivery, small head circumference and low birth weight and impaired neurophysiological development[30].

During the first trimester of pregnancy, there is a two-fold or three-fold increase in the Thyroglobulin due to stimulation by the circulating estrogen level. It lowers the free T4 and T3 concentrations. The human chorionic gonadotropin (hCG) stimulates the thyroid gland in late first trimester[31]. It reduces the TSH levels mostly between 8 and 14 weeks of pregnancy. Later in the second trimester alterations occur in the peripheral metabolism of the thyroid hormones. The enzymes, Type I, II and III deiodinases acts during this phase. Type II is present in the placenta and causes T3 production locally, which is fatal when maternal T4 production is reduced. It can also affect the fetal thyroid metabolism [30].

3.4.7. Fetal Thyroid Physiology

Thyroid gland appears as a midline out pouching from the anterior pharyngeal floor and reaches its position by 7 weeks of gestation. The iodide trapping is detectable at 12 weeks and the first T4 production starts by 14weeks. TRH is detectable by 8 to 9weeks and Pituitary portal circulation by 10 to 12 weeks. The concentrations of T4 and T3 rise from 20weeks to term. Fetal TSH will rise from 4 to 8mU/L between 12weeks and term. Most of

the fetal T4 is converted to T3 and used for the development of the tissues like brain. Local T4, in which T3 is formed by type II deiodinase. Only limited quantities of T4 and T3 transferred from mothers to the infants through the placenta and the T4 transfer occurs mostly in the second trimester of pregnancy. Immediately after birth, there is an increase in TRH and TSH followed by an increase in the T4 levels in the fetus. It will return to normal adult values by 6 weeks of age [30].

3.4.8 Effects of Hypothyroidism in mothers in pregnancy

Women with hypothyroidism have:

- Decreased fertility
- More risk of abortion
- Gestational hypertension
- Anaemia
- Abruption placenta
- Increase in postpartum haemorrhage

3.4.9 Effects of hypothyroidism in infants

It includes:

- Preterm birth
- Low birth weight
- Respiratory distress
- Mental retardation
- Low Intelligent Quotient[32].

3.5 PHYSIOLOGY OF HUMAN AUDITORY SYSTEM

3.5.1. Cochlear transduction: Endocochlear potential in the scala media has a positive potential of +80 mV relative to that of perilymph. The hair cell has a negative potential when compared to perilymph, -70 mV, so there is a potential difference of 150 mV between the endolymph and the hair cell[25].

The travelling wave of sound bends both the basilar membrane and the tectorial membrane. This occurs in different axes, the displacement moves the tectorial membrane causes a shearing action on the hair cells. This causes a resistance of hair cell with the endolymph and changes the amount of current flowing in the cell. Thus the movements of the cochlear partition help in the flow of current through the hair cell body. This helps in excitation of the afferent nerve endings[25].

3.5.2 Cochlear nerve activity: The nerve acts on 'an all or none' basis. At rest, all the cochlear nerve fibres are discharging. Each nerve fibre responds most readily to a stimulus of a particular frequency. Tuning curve of acoustic nerve fibres shows that frequency sensitivity is much finer or the tuning much sharper, than the mechanical response of the basilar membrane. The tuning curves overlap at high intensities[25].

The tuning curves of low-frequency fibres are symmetrical but fibres for high frequencies are asymmetrical with a high-frequency cutoff. Thus the sound intensity is by the rate of the spike discharge and the number of active fibres. Frequency is from the site of more excitation and from the spatial pattern and responses of excited fibres. At very low frequencies, the rhythm of discharge is noticeable but at higher

pitches phase locked information in groups of fibres extends the potential of volley theory information. The frequency and intensity of the impulse rates are finally separated centrally by the activity of 10^7 neurons in the brain with which the auditory fibres eventually connect[25].

3.5.3 Cochlear microphonics: The alternating potentials are present in the hair cells, due to sound stimulus and the movements of cochlear partition. They persist after nerve conduction ends and appear as responses in opposite senses with the upward and downward movement of the partition. Summating potentials show as steady baseline shifts in the recording. They reflect steady changes in endocochlear potential[25].

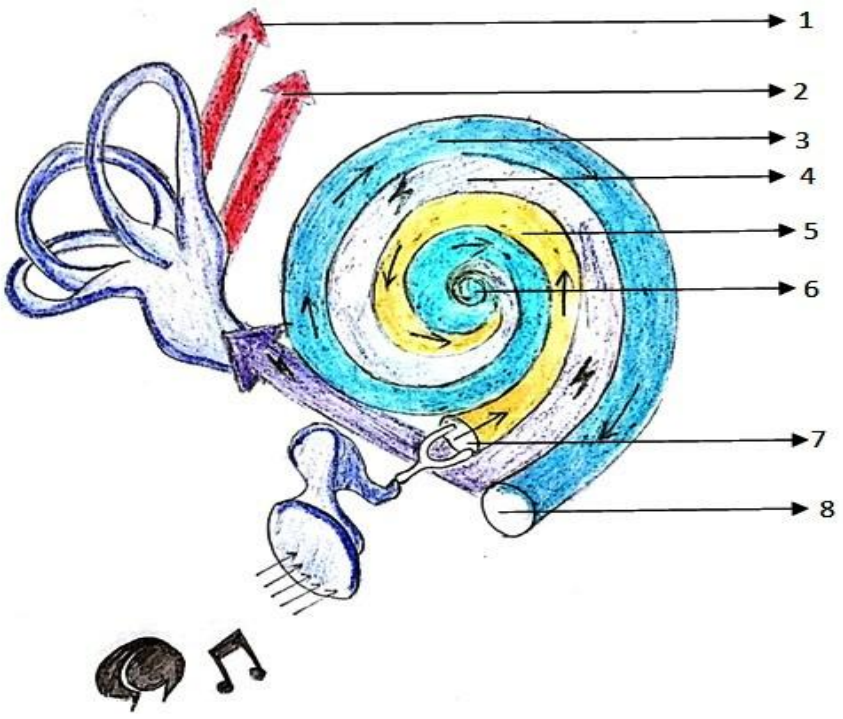


Figure 7: Showing the transmission of sound. (1-Vestibular Nerve,2- Cochlear Nerve, 3-Scala Tympani, 4- Scala Media, 5-Scala Vestibuli, 6- Helicotrema, 7- Oval window, 8-Round window).

3.6. THYROID ANTIBODIES

Some people develop antibodies against their own thyroid tissues (Autoimmune thyroiditis). Hashimoto's thyroiditis has increased level of anti-thyroid antibodies in blood[9].

Thyroid antibodies include:

- Thyroid peroxidase antibody (TPO)- If the level is less than 60U/ml is taken as normal.
- Thyroglobulin antibody (TGAb)
- Thyroid stimulating hormone receptor antibodies (TSHRAb)- including thyroid stimulating immunoglobulin(TSI) and thyroid binding inhibitory immunoglobulin(TBII).[9]

  A study conducted in Paris in 2014 showed a free passage of thyroperoxidase antibodies through the umblical cord from the mother to the fetus, affecting the fetal thyroid morphology and physiology [10].

3.7 MEDICATIONS

The medications are given to replace the deficient thyroid hormone production and to treat symptoms associated with severe hypothyroidism[30].

3.7.1. LEVOTHYROXINE

The medication of choice for hypothyroidism is Levothyroxine. It is well taken up with a half-life of 7 days which allows once a day administration. The T3 and T4 levels will

be stabilized in about 6 weeks. The starting dose is influenced by the age, history of coronary heart disease and cardiac arrhythmias. A starting dosage of 1.5 μg/kg/day, in a healthy patient is given, but in elderly patients or those with cardiac disease, a starting dose of 25 μg to 50μg per day is adequate. Correct dosage is important to maintain the euthyroid state[33].

3.7.2. LIOTHYRONINE

Liothyronine (L-triiodothyronine) is rarely used as a single medication for hypothyroidism especially in elderly patients and those with cardiac diseases. It rapidly increases its concentrations in the body. It is used along with levothyroxine when needed to reduce the symptoms[38]

The TSH has to be repeated after 6 to 8 weeks of Thyroxine therapy. Thyroid hormonal levels are strictly checked in women who are pregnant and in children with hypothyroidism to prevent adverse effects. Once the dosage is stabilized TSH can be repeated once in 6 months[33]

3.8 HYPOTHYROIDISM AND HEARING

In 1883, Bircher first demonstrated the relation between hypothyroidism and hearing impairment. The hypothyroidism induced hearing loss first gained acceptance when the London clinic Institution Committee of Myxoedematous documented that 50% of hypothyroid patients had hearing loss. Several studies showed that retrocohlear, endocochlear or central hearing ways can be adversely affected in patients with hypothyroidism[34].

In 1989, it was found that prolongation in the I-III and I-V interpeak latencies in BERA occurs in hypothyroid patients. Some studies found prolongation in all frequency latencies and interpeak latencies can occur in hypothyroidism on BERA. Studies detected bilateral moderate sensorineural hearing loss in about 40% of the hypothyroid patients. In 2008 it was found that retrocochlear hearing loss in hypothyroid patients [34].

In newborn mice hypothyroidism was induced by the use of radioactive iodine and by usage of Propylthiouracil, showed gross changes in the inner ear hearing. These changes include changes in the bullae and cochlea, alterations in the middle ear ossicles. Stapes was commonly affected with distortion of fusion of stapes with incus. Morphological variations of the internal ear were documented. These were disruption of the tectorial membrane, distortion of the hair cells, deposits in the Hensen cells, debris and acidophilic deposits in the cochlear duct and enlarged intracellular spaces in stria vascularis. Therefore hearing loss associated with hypothyroidism can be conductive, sensorineural or mixed hearing loss[34].

The hearing loss induced by hypothyroidism can be reversible by timely treatment. The common otological symptoms of hypothyroidism are hearing loss, tinnitus and dizziness[34].

3.9 ASSESSMENT OF HEARING FUNCTION

Assessment of hearing is needed to evaluate hearing impairement. Hearing tests can be behavioural and objective. Behavioural tests require the cooperation of the participant. They include pure-tone audiometry and speech-discrimination tests, mostly done in adults and older children. The infants are observed for changes in behaviour in response to sound[35].

Objective hearing tests do not require active cooperation from the participant. They are suitable for hearing assessment in newborns. They include middle-ear tests, Auditory Brain Stem reflexes and Otoacoustic emissions [35].

3.9.1 NEONATAL SCREENING

The universal newborn hearing screening (UNHS) is done for the early detection of hearing loss and for the initiation of early interventions. Newborn screening (NBS) is made to screen the infants for rare congenital conditions, which can result in morbidity and mortality for the infants and to improve the health outcome for those infants[36].

The prevalence of neonatal hearing loss is more than twice that of other newborn disorders. Bilateral Congenital hearing loss is seen in approximately 1 to 5 per 1000 live births and unilateral hearing loss increases up to 8 per 1000 live births. In India, 1 to 8 per 1000 infants screened to have neonatal hearing loss. Early detection and treatment for hearing loss within 6 months of age provide better development in language, academics and also in their social life [37].

Newborn hearing screening is done by automated otoacoustic emission (OAE) tests and is confirmed by automated auditory brainstem response (ABR) tests. Newborns who fail the automated ABR test are referred for a more comprehensive diagnostic ABR test. OAE is simple, cheap, quick and reliable method with 100% sensitivity and specificity of 99 %. The advantages of ABR include identification of neonates with nerve deafness (retrocochlear) and high sensitivity and specificity[37].

3.9.1.1 Otoacoustic emissions: Otoacoustic emissions (OAEs) are low intensity sounds from a normal-functioning cochlea. They were first reported by Kemp in 1978. The sounds produced are transmitted by the middle ear and is assembled by a microphone in the external auditory canal. OAEs are generated from two distinct mechanisms: an active non-linear component involving the outer hair cells, and a passive linear reflection of the travelling wave along the basilar membrane.

The two categories of OAEs include Spontaneous and Evoked. Spontaneous OAEs occur without external stimulation. They are stable pure tones at about −10 to +30 dB SPL and are seen in 40% of healthy individuals [50]. They have limited clinical significance since they cannot be measured and occur at discrete, unpredictable frequencies. Evoked OAEs occur in response to an external stimulation. The stimuli that are commonly used for evoking OAEs can be either: clicks or tone bursts which generate transient evoked OAEs (TEOAEs), and pairs of primary tones (*f*1, the lower-frequency pure tone, and *f*2, the higher-frequency pure tone) which generate pure-tone distortion product OAEs (DPOAEs) due to the non-linearity in the cochlea. DPOAEs either diminishes or eliminates at the frequencies which correspond to the region of hearing loss and as such are able to give better frequency-specific assessment than TEOAEs. "The intensity of the detected OAE response to the intensity of the noise measured in the canal is the signal-to-noise ratio (SNR)", which is used to determine the presence or absence of OAEs in neonatal ears[38].

OAE detection relies on both forward and reverses transfer of sound signals. Acoustic stimuli that provoke the production of OAEs are transmitted forward to the inner ear via the external and middle ear, while the evoked OAEs are transmitted in the reverse direction. This

makes the test critically dependent on the middle-ear status so that departures from the normal functioning of the middle ear have more impact on the OAEs than on the ABR. Major limitation of the OAE test is due to its dependence on the middle and external ear. Therefore OAE test has high false-positive rates. The middle ear with any amniotic fluid and mesenchyme can give false positive results up to 20th day after birth[38].

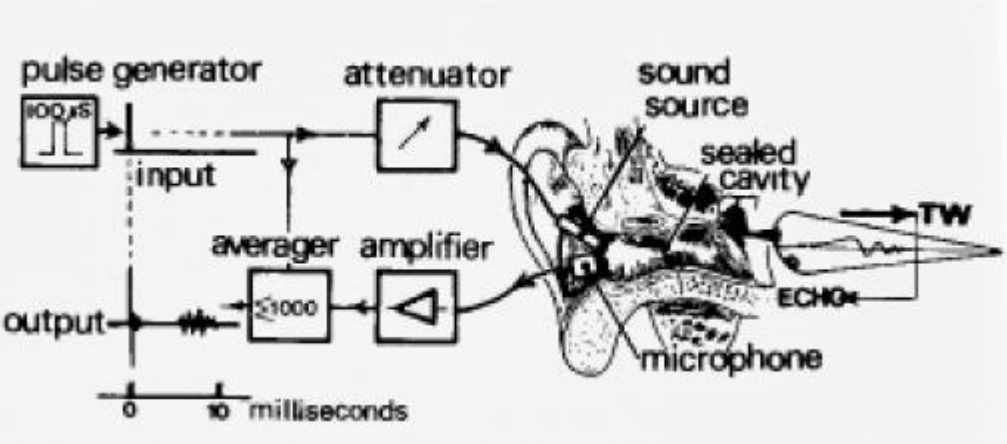


Figure 8: Showing the principal of OAE

The OAE equipment used for hearing screening is automated to generate a pass or fail results based on the SNR value for a given number of frequencies. Most equipment accepts an SNR of between 3 and 7 dB at 3 out of 4 tested frequencies for a pass[38].

3.9.1.2 Auditory Brain stem Response [ABR]: ABR is a measure of auditory synchrony along the auditory pathway. It is an evoked response arising from the auditory pathway. The ABR test is the most common form of electrophysiological hearing testing. The seven waves of the ABR determine the functioning of the central auditory pathway and also the threshold of hearing.[13]

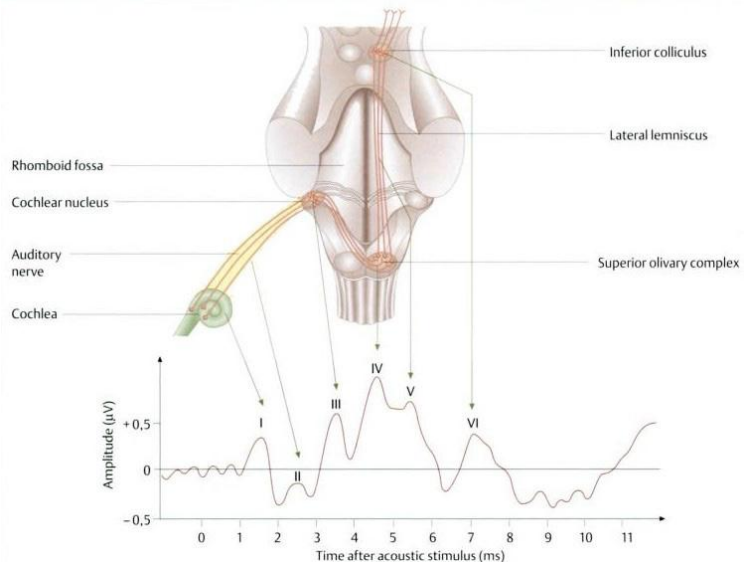


Figure 9: Showing the waves of BERA and Auditory Pathway

The ABR is present from the 25th week of gestation. The Automated ABR test uses stimuli at 30-40 dB SPL intensity which evoke a response wave-form that is then matched to a template by an algorithm within the screening device. The congruence of the response to the template is used to determine the status as pass or fail of the infant.

The BERA consists of waves that reflect the activation of the auditory pathway. At low stimulus all seven waves is present and at faster rates only wave V is seen in adult[55].

Infants are tested when they are in their natural sleep. Passage of the impulse through the auditory pathway generates an electrical activity which can be monitored by placing a surface (far-field) electrode on the vertex of the scalp. On the graphic recording, this electrical activity presents a waveform with discrete peaks, and dependent on the functional and structural integrity of the auditory pathway.[13]

The process of measuring the electrical activity in the brain in response to a sound stimulus presented to the ear is very complicated, because some degree of random and spontaneous electrical activity is continually occurring within the brain. A recording of this random electrical activity is called Electroencephalography (EEG). The electrical activity in the brain, in response to a sound stimulus mixes up with the random and spontaneous electrical activity occurring within the brain, and is difficult to trace on EEG[13].

It has five prominent peaks and two small peaks. These are the BERA potentials. They have troughs and crests, termed as BERA waves. The waves are numbered from I to VII and each of these waves gives information about a specific segment of the auditory pathway. Hence for proper interpretation of the BERA graph, the different waves especially the waves III and V have to be accurately identified[13].

Wave	Site of Neural Generator
I	Cochlear Nerve (distal end)
II	Cochlear Nerve (proxmimal end)
III	Cochlear Nucleus
IV	Superior Olivary Complex
V	Lateral Lemniscus and Inferior Colliculus
VI & VII	Neural Generators not definitely known.

Figure 10: showing the representation of BERA waves

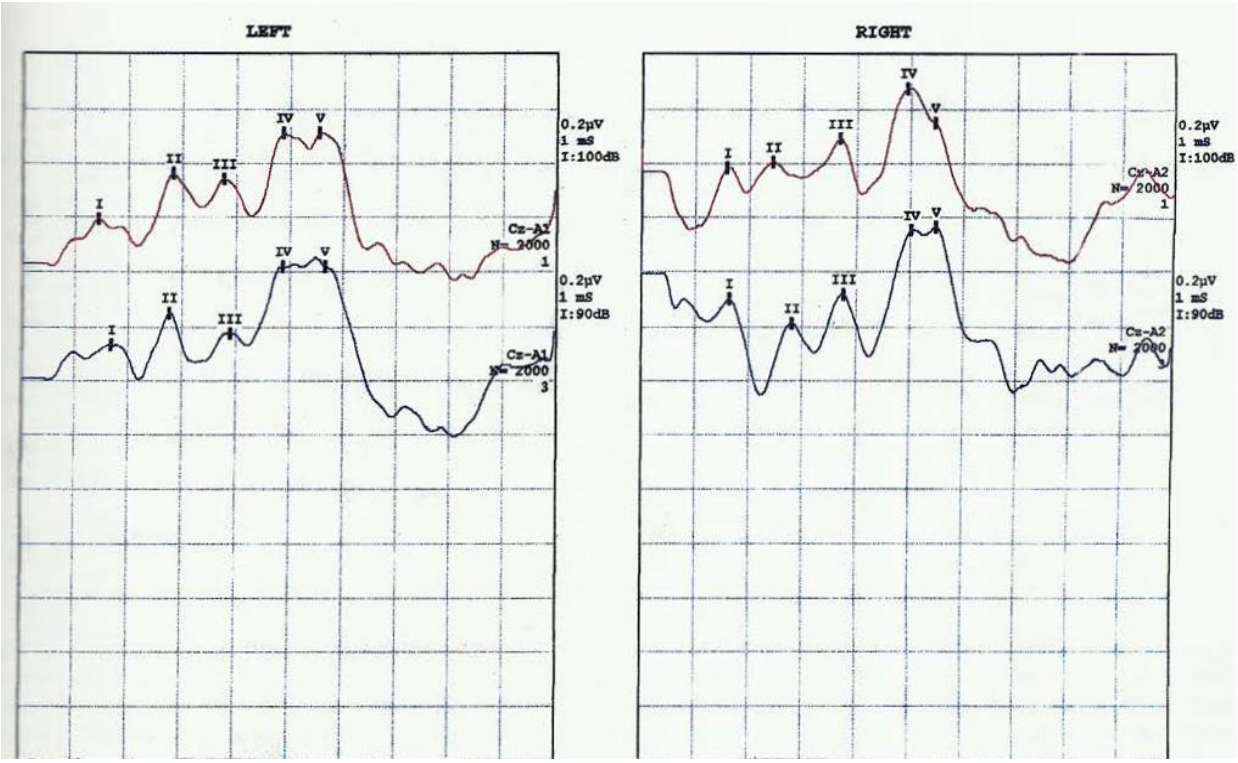


Figure 11: showing the graphical representation of BERA

BERA is objective and an authentic method for assessing newborn hearing. However, it is complex and costly, requiring expensive machine and a trained audiologist. It is a non-invasive procedure and a more standardised parameter than electrocochleography.

Brainstem evoked response audiometry test is useful in:

- Identification and quantification of deafness in non-cooperative patients. It can be done in deeply anaesthetized patients;
- Determines the nature of deafness (whether sensory or neural) in non-cooperative patients.
- Identification of retro-cochlear pathologies.

- Study of central auditory disorders; and

- Maturation of the central nervous system in newborns and prognosis in a comatose patient[13].

MATERIALS AND METHODS

IV. MATERAILS AND METHODS

The study was done in infants born to hypothyroid (including subclinical hypothyroidism) women or treated for hypothyroidism during pregnancy and euthyroid women presenting to the Department of Obstetrics and Gynaecology and Department of Pediatrics in R L Jalappa Hospital &Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar from December 2016 to April 2018.

SAMPLE SIZE ESTIMATION:

The sample size was calculated with the prevalence of hearing loss in infants born to hypothyroid women (10%) and euthyroid women (2%) from a previous study conducted in Northwest India.[39]

- Sample size= $\{2pq\ (Z_a+Z_b)^2\}/(p1-p2)^{2.}$
- P1=prevalence of hearing loss in infants born to hypothyroid women
- P2=prevalence of hearing loss in infants born to euthyroid mothers
- P=average of p1 and p2
- Z_a=1.96 which is the Z statistic for alpha error of 5%
- Z_b=0.84 which is the Z statistic for beta error of 20%
- Using the above values at 95% confidence level a sample size of 140 infants born to hypothyroid women and 140 infants born to euthyroid women were included in the study.

INCLUSION CRITERIA

All infants born to hypothyroid (including subclinical hypothyroidism) women or treated for hypothyroidism during pregnancy and euthyroid women presenting to the

Department of Obstetrics and Gynaecology and Pediatric outpatient department of R L Jalappa Hospital & Research centre from December 2016 to April 2018.

The study done with **the approval of the Institutional Ethical Committee** and parents/caregivers were explained about the importance of the study and a written informed consent was taken.

EXCLUSION CRITERIA

Infants with the following conditions were excluded from the study:-

- Infants with hearing loss due to otitis media or any other ear infections;
- Hyperbilirubinemia requiring phototherapy;
- Very low birth weight (below 1.0 kg);
- Birth asphyxia requiring ventilatory support;
- Craniofacial dysmorphism;
- Use of any ototoxic medications in infants;
- Any history of familial hearing loss;
- Infants with syndromic hearing loss
- Infants born to women with overt or gestational diabetes mellitus.

GENERAL PHYSICAL EXAMINATION

The infants were subjected to general physical examination after obtaining a written informed consent from the parents/caregivers. Detailed clinical history was taken including family history of hypothyroidism, usage of any ototoxic drugs and history of any radiation

exposure. Detailed prenatal, natal and post natal history was taken. The detailed systemic examination was also done on all infants.

OTOLOGIC EXAMINATION

All infants underwent detailed otological examination including the inspection of the preauricular area, post auricular area and External Auditory Canal, to look for any congenital deformities. All infants were examined for the presence of any remnants of amniotic fluid in the external ear as it can cause changes in the audiological evaluation especially with otoacoustic emissions which is dependent on the status of the external and middle ear. Status of the Tympanic membrane was also evaluated, as the infants are more prone to develop acute otitis media secondary to frequent upper respiratory tract infection. Facial Nerve was also examined in detail for its integrity and function.

ESTIMATION OF HORMONE LEVELS

Thyroid hormones levels, T3, T4 and TSH in the mothers and TSH of infants were checked and were noted. Free T3, T4 and TSH of the women were done routinely in all trimesters of the pregnancy, and the values were documented. According to these values; the dose of the Thyroxine was titrated and was administered for hypothyroid women. The normal value of T3 was taken between 0.7-2.0ng/mL, T4 between 6.0-11microg/dL and TSH between 0.4-5.0microIU/mL for the mother. In infantsT3, T4 and TSH were checked at the time of birth and the values were collected and analysed. Normal range was taken between 1.0-39.0microIU/mL.

ESTIMATION OF ANTI-TPO ANTIBODIES

The Thyroperoxidase antibody levels were checked in 4 infants born to women diagnosed with hypothyroidism in the postpartum period, at 4th month of life by Chemilumescence method and the values were documented. The blood samples were send to a laboratory in Bangalore. The value less than 60U/mL were taken as negative.

DEVELOPMENTAL HISTORY

Developmental milestones of all the infants were assessed in terms of attaining social smile at the 2nd month of life and attainment of complete head control at the 4th month of life.

AUDIOLOGICAL EVALUATION.

After a detailed general physical examination and ear examination, all infants were subjected to audiological evaluation. It was carried out with Otoacoustic emissions (OAE) and Auditory Brainstem Response (ABR) at the 1st month and the 4th month of life.

OTOACOUSTIC EMISSIONS:

AUDIO screener from GSI (Grason Stadler Incorporation) was used for OAE testing which is a hand-held battery-operated screening device. Infants were scheduled for testing when they were in their natural sleep. The test done in a sound treated room to reduce any ambient noise interfering with the test. A suitable probe tip depending on the size of the ear canal opening was selected and coupled to the OAE probe. The probe tip was inserted sufficiently deep in to the ear canal till a good seal of the probe is obtained.

DPOAE were used to test the infants, wherein acoustic stimuli were delivered through the loudspeaker and frequency specific response (at 2000Hz, 3000Hz, 4000Hz, 5000Hz and 6000Hz) were recorded through microphone. Each ear was tested separately. The results were noted as either "pass" or "refer" based on the functional status of Outer Hair Cells. A "Pass" outcome means that the child has normal outer hair cell function whereas, 'Refer' OAE can mean that a) the child has a potential hearing loss or, b) the child may have middle ear problems that affects the ability to record a response from the inner ear.

AUDITORY BRAINSTEM RESPONSE:

A 2 channel Smart EP by Intelligent hearing Systems (IHS) was used for ABR testing. For performing ABR on infants, the skin of forehead and both mastoid was cleaned and electrodes were placed. The electrode on the anterior fontanelle (Fz) served as positive electrode. The electrode on the mastoid (M_i) served as the negative electrode on the test ear and the forehead electrode (Fpz) as reference electrode. Once the electrodes were connected, the electrode impedance was checked. The impedance was monitored to be less than 5 kΩ for all the electrodes and inter-electrode impedance to be less than 2 kΩ. Click stimuli of rarefaction phase was presented through the insert ear phone, to stimulate the auditory system, one ear being tested at a time. Filter settings was kept between 30-3000Hz and a repetition rate of 30.1/sec was used. Analysis time was set at 25 milliseconds.

The hearing threshold is defined as the 'minimum intensity needed to elicit wave V. To determine the threshold, the intensity of the stimulus was gradually reduced from a higher intensity till wave V is not identifiable. ABR was acquired twice at each intensity to look for the replicability of the waveform. Replicable wave V present at 30dB nHL was taken as

normal hearing whereas replicable wave V present at 40-90 dBnHL was considered as mild to severe hearing loss. For analysis, the latency (in milliseconds) at which wave V appeared at 30dBnHL was noted and compared between study and control infants.

Figure 12: Showing performing of OAE in the infant

Figure 13: Showing the setting up of BERA

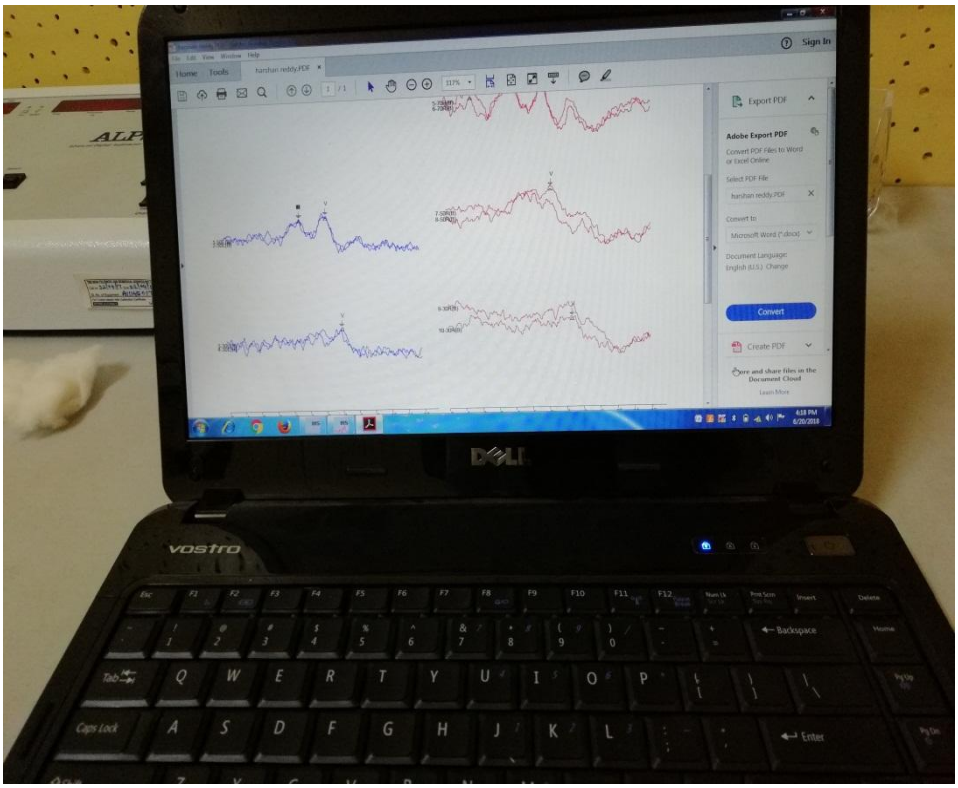


Figure 14: Showing replication of wave V

FOLLOW-UP

Infants were called at the 4th month of life and Otoacoustic Emissions and Brain Stem Evoked Response Audiometry was repeated. Two infants were followed upto 6th and 8th month respectively because of the absence of wave V in BERA at 1st and 4th month of life.

TESTS IN CONTROL GROUP

Detailed evaluation of infants born to euthyroid women was done. They also underwent audiological evaluation using Otoacoustic emissions and Brain stem Evoked Response audiometry and the results were documented.

Otoacoustic emission values and brainstem response audiometry results were documented and compared between infants born to hypothyroid (including subclinical hypothyroidism) women or treated for hypothyroidism during early and late in pregnancy and euthyroid women.

STATISTICAL ANALYSIS:

Data was entered into Microsoft excel data sheet and was analysed using SPSS 22 version software. Categorical data was made in the form of Frequencies and proportions. **Fischer's exact test** was used as a test of significance for qualitative data. Continuous data were showed as mean and standard deviation.

Graphical representation of data: MS Excel and MS Word were used to obtain various types of graphs such as bar diagram.

p value (Probability that the result is true) of <0.05 was statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

OBSERVATION AND RESULTS

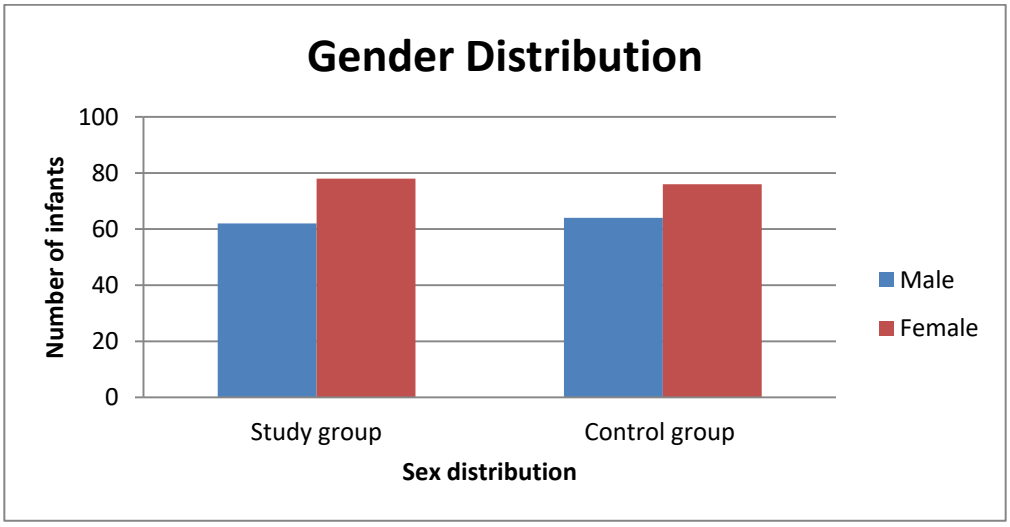
V. RESULTS

Our study done in 140 infants born to hypothyroid women and 140 infants born to women with no comorbidities from a period of December 2016 to April 2018. All infants underwent general physical and otological investigations. Otoacoustic emissions and Brainstem Evoked Response Audiometry was done in all infants at the 1st month of life. All infants were followed up to the 4th month, one infant upto 6th month and other infant at the 8th month of life. Developmental milestones were evaluated in terms of attainment of a social smile at 2months of age and proper head control by the 4th month of age.

SEX DISTRIBUTION

SEX	**Study group** N (%)	**Control group** N (%)
Male	62 (44.3)	64 (45.0)
Female	78 (55.7)	76 (54.3)

Table 3: Showing gender distribution in the study



Graph 1: Showing gender distribution among the study group and control group.

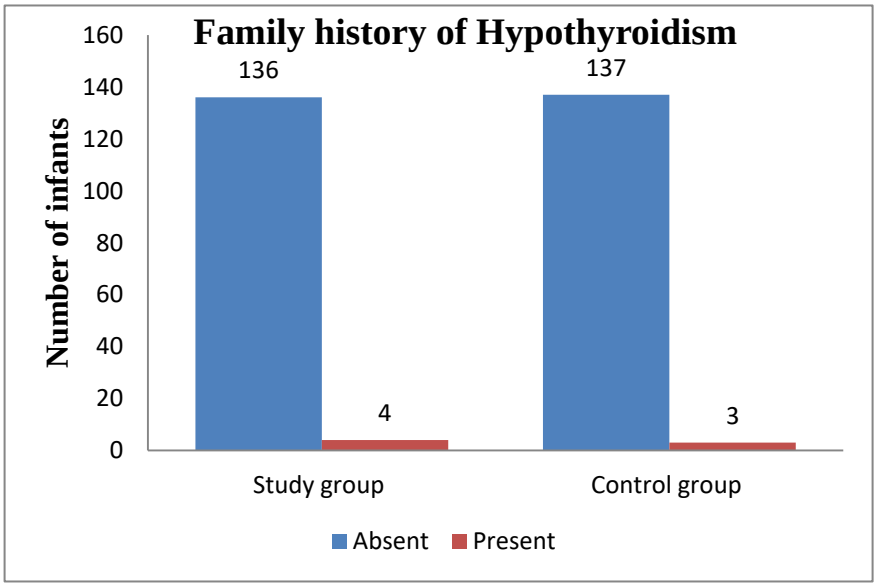
In the study group, 44.3% were male infants and 55.7% were female infants. In the infants born to euthyroid women 45.7% were males and 54.3% were females as shown in Table: 3.

FAMILY HISTORY OF HYPOTHYROIDISM

Among the study group, 4 patients had a history of hypothyroidism in the family and among control group 3 patients had a family history of hypothyroidism.

Family History of hypothyroidism	**STUDY GROUP N (%)**	**CONTROL N (%)**
Absent	136(97.1)	137(97.9)
Present	4(2.9)	3(2.1)

Table 4: showing the history of hypothyroidism in the family



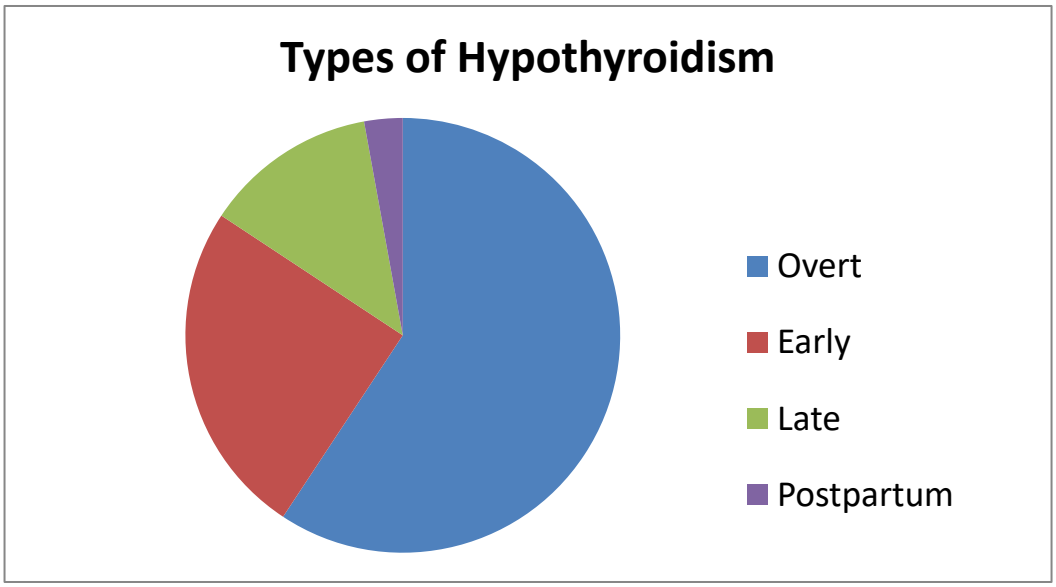
Graph 2: Presence of family history of hypothyroidism among the study and control group.

TYPES OF HYPOTHYROIDISM

In the present study, 83 women had a history of overt hypothyroidism that is they had a history of hypothyroidism before pregnancy. In the first 6months of pregnancy, about 35 patients were detected to have hypothyroidism and 18 patients during the last trimester. During the post-partum period within 6months, 4 patients had hypothyroidism among them 2 had a history of Hashimotos Thyroiditis.

TYPES OF HYPOTHYROIDISM DETECTED DURING PREGNANCY	N (%)
Overt	83 (59.3)
Early	35 (25.0)
Late	22 (15.7)

Table 5: Showing the types of hypothyroidism in the study group



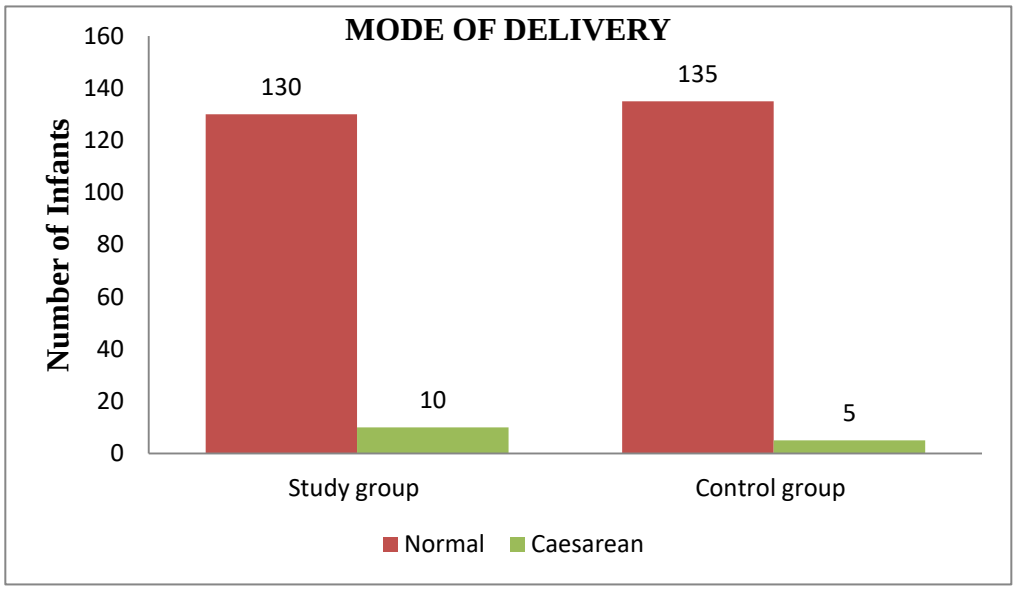
Graph 3: Showing the frequency of overt, early, late and postpartum hypothyroidism in our study.

MODE OF DELIVERY

All the mothers attended the study had normal hospital among them 10 in the study group and 5 in control group had caesarian sections.

MODE OF DELIVERY	Study group N (%)	Control group N (%)
Normal	130(92.9)	135(96.4)
Caesarean	10(7.1)	5(3.6)

Table 6: Showing the mode of delivery



Graph 4: Showing the mode of delivery among the study group and control groups.

All women took Thyroxine for the correction of Hypothyroidism during pregnancy except those 4 women who were detected at the time of delivery. Free T3, Free T4 and TSH levels of the women were regularly tested and a dose of the Thyroxine was titrated accordingly.

All infants underwent a thorough general physical and otological examination and were normal. In the study group, infants had birth weight of 2.52±0.47 and in control group

was 2.63+/-0.40, slightly lower but not clinically significant. All had a good APGAR score (at 1 minute 7 and at 5 minutes 9). TSH levels were normal in all infants. In 5 infants the level of Anti-TPO antibodies were checked at the 4th month of life and were below 60uI/mL and were normal. All infants attained social smile at 2 months of age and good head control at the 4th month of life. No global developmental delay was noticed in any infants.

HORMONAL LEVELS	Case (N=140)	Control (N=140)
Free Triiodothronine(Mean ± SD)	1.42 ± 0.28	1.48 ± 0.27
Free Tetraiodothyronine(Mean ± SD)	7.83 ±1.51	7.88 ± 1.26
Thyroid Stimulating Hormone (Mean ± SD)	2.23 ±1.06	2.71 ± 0.63
Dosage of Thyroxine (Mean ± SD)	38.20 ±19.73	0.0000
Term of Gestation (Mean ± SD)	38.40 ± 0.71	38.34 ± 0.53

Table 7: Showing the level of free T3, T4 and TSH in women, Thyroxine dosage and term of Gestation

INFANT PARAMETERS	Study group(n=140)	Control group(n=140)
Birth weight (Mean ± SD)	2.52 ± 0.47	2.63 ± 0.40
Thyroid Stimulating Hormone (Mean ± SD)	10.90 ±1.01	0.0000
Pulse (Mean ± SD)	130.07 ± 3.75	130.37 ± 3.5
Respiratory rate (Mean ± SD)	49.55 ± 4.44	49.47 ± 4.24

Table 8: Showing the infant characteristics.

AUDIOLOGICAL EVALUATION

All infants in the study group and control group underwent audiological evaluation using Otoacoustic Emissions and Brainstem Evoked Response Audiometry at the 1st month and followed at the 4th month of life.

OTOACOUSTIC EMISSIONS

DPOAE screening was done and "Pass" or "Refer" findings were noted across different frequencies, 2000Hz, 3000Hz, 4000Hz, 5000Hz and 6000Hz, for the right and left ear separately. Overall, OAE outcome was considered to be "pass" when 3 or more frequencies out of 5 frequencies showed pass and was considered "refer" when three or more frequencies showed refer. OAE recordings are shown in the table below. This was documented at 1st and 4th month of life in both study group and control group.

OTOACOUSTIC EMISSION RESULTS AT 1ST MONTH

		Study group N (%)		Control group N (%)	
2000Hz_OAE		**Right**	**Left**	**Right**	**Left**
Pass		107(76.42)	107(76.42)	140(100)	140(100)
Refer		33(23.6)	33(23.6)	0	0
3000Hz_OAE					
Pass		115(82.1)	115(82.1)	140(100)	140(100)
Refer		25(17.9)	25(17.9)	0	0
4000Hz_OAE					
Pass		115(82.1)	115(82.1)		140(100)
Refer		25(17.9)	25(17.9)		0
5000HZ_OAE					
Pass		140(100)	140(100)	140(100)	140(100)
6000Hz_OAE					
Pass		140(100)	140(100)	140(100)	140(100)
OVERALL	**REFER**	**6**		**0**	
	PASS	**134**		**140**	

Table 9: OAE results at 1st month of life including both the study group and control group.

OTOACOUSTIC EMISSIONS AT 4TH MONTH OF LIFE

		Study group N (%)		Control group N (%)	
2000Hz_OAE		**Right**	**Left**	**Right**	**Left**
Pass		131(93.5)	131(93.5)	140(100)	140(100)
Refer		9(6.4)	9(6.4)	0	0
3000Hz_OAE					
Pass		140(100)	140(100)	140(100)	140(100)
4000Hz_OAE					
Pass		140(100)	140(100)	140(100)	140(100)
5000Hz_OAE					
Pass		140(100)	140(100)	140(100)	140(100)
6000Hz_OAE					
Pass		140(100)	140(100)	140(100)	140(100)
OVERALL	**REFER**	**0**		**0**	
	PASS	**140**		**140**	

Table 10: OAE results at 4th month of life including both the study group and control group.

BRAINSTEM EVOKED RESPONSE AUDIOMETRY

All infants underwent BERA after OAE at 1st and 4th month of life. The presence of replicable wave V at 30dB nHL was checked in all the infants. Number of infants with present/absent wave V is given below.

		Present wave V at 30dBnHl N (%)	Absent wave V at 30dBnHl N (%)
Study group	**Right**	138(98.5)	2(1.42)
	Left	138(98.5)	2(1.42)
Control group	**Right**	140(100)	Nil
	Left	140(100)	Nil

Table 11: Showing ABR at 1st month of life in study and control group

		Present wave V at 30dBnHl N (%)	Absent wave V at 30dBnHl N (%)
Study group	**Right**	138(98.5)	2(1.42)
	Left	138(98.5)	2(1.42)
Control group	**Right**	140(100)	Nil
	Left	140(100)	Nil

Table 12: Showing ABR at 4th month of life in study and control group

As evident in the table above, all infants in the control group had replicable Vth peak at 30dBnHL. However, only 2 infants had absent wave V at 30dBnHL in the study group even at 4th month of life. Hence these infants were evaluated in later months. Among the 2 infants, one infant showed replicable wave V at 30dBnHL at 6th month and in another infant the replicable wave V started appearing at 8th month of life at 7.32 and 7.43milliseconds. Thus it showed no hearing loss in the study group, although there was delayed appearance of wave V in 2 infants. Further the latency at which Vth peak was seen noted in all infants in both the groups and the mean latency is tabulated below. Mean latency was found to be delayed in the study group when compared to control group.Around 50% of the infants in the study group showed a prolongation of the latencies of wave V replicability at 30dBnHL in BERA in 1st month of life when compared to control group. However by the 4th month of life

it had got corrected. Similarly infants having family history of hypothyroidism and also infants born to women who diagnosed to have hypothyroidism during the postpartum period showed a prolongation in the mean latency period. However, on comparing between the groups, it was found that the difference was not statistically significant (p=0.498, not less than 0.05)

	Study group (N= 140)	**Control group (N= 140)**
BERA-_left ear (Mean ± SD)	8.03± 0.60	7.78±1.23
BERA-right ear (Mean ± SD)	8.05±0.58	7.96±1.18

Table 13: Showing the mean latency of replicability of Vth peak at 30dBnHl at 1st month

	Study group (N= 140)	**Control group (N= 140)**
BERA-left ear (Mean ± SD)	8.12±5.45	7.59±1.01
BERA-right ear (Mean ± SD)	7.67 ±0.41	7.62 0.01

Table 14: Showing the mean latency of replicability of Vth peak at 30dBnHl at 4th month

Group	**INFERENCE**		p value
	Within Normal Limits	**Delayed**	
Study group	138 (98.6)	2 (1.4)	0.498 *
Control group	140 (100)	0	
* Fishers exact test			

Table 15: Showing the inference of the study and control group

DISCUSSION

VI. DISCUSSION

Maternal hypothyroidism is known to cause hypothyroidism in infants. Even after implementation of screening programs there is a rise in sensorineural hearing loss in infants with Congenital Hypothyroidism.[40] There are hardly any studies showing the hearing outcome in infants born to women whose hypothyroidism was corrected during pregnancy and also in subclinical cases. Anti Thyroperoxidase antibodies crosses the placenta from mother to infants and was proven in a study in Paris in 2014, especially in women with Hashimotos thyroiditis.[10] In animal (mice) models, there was a delay in development due to these antibodies. The hormonal and immunologic variations during pregnancy and at the time of birth and the dependence of the fetus on maternal iodine and thyroid hormones can significantly influence the infants. Thyroxine is needed for the development of structures of ear, maturation of the peripheral and central auditory pathway[41]. Newborn screening for hearing is important as it helps in early detection so that initiation of treatment and rehabilitation is early. The commonly used screening method for hearing is Otoacoustic emissions and is confirmed by Auditory Brainstem Response analysis.[36] Therefore our study was conducted to evaluate the hearing outcome in infants born to women whose hypothyroidism was corrected during the pregnancy.

In our study we enrolled 280 infants, 140 infants born to women with overt hypothyroidism, treated for hypothyroidism in the early and late part of pregnancy or detected during the time of birth and 140 infants born to euthyroid women. The study period being April 2016 to April 2018. All infants underwent audiological evaluation using

Otoacoustic emissions and Brain stem evoked response audiometry at 1st month and were followed up to 4th month of life.

In the study there was no significant gender predilection, however female infants were more. The latest WHO statistics showed an increase in male infants when compared to females. Studies done in various parts of India also showed more number of male infants when compared to female infants in the general population.[43]

The age, gender and family history can influence the incidence of thyroid disease in infants especially in autoimmune disorders.[44] In the study, 4 patients in our study group and 3 patients in our control group had family history of hypothyroidism. A study on genetics influencing thyroid function showed that 67% of the circulating thyroid hormones and TSH is genetically determined.[45] They can influence a wide range of thyroid dysfunctions. In 2013 a study done to evaluate the factors influencing the thyroid disorders showed more than 50% positivity for family history.[44]

Hypothyroidism is a common endocrinological abnormality during pregnancy. It can be either overt or subclinical cases. During pregnancy it can be detected during the early and late part of pregnancy or at the time of birth. The important cause of hypothyroidism in pregnancy associated with the presence of autoimmune antibodies is Hashimotos thyroiditis.[30]

In our study 59.3% of the pregnant women had overt hypothyroidism, 25.0% of them were detected to have hypothyroidism during the first three months of pregnancy and12.9% had hypothyroidism in the third trimester. At the time of birth, 4 women had hypothyroidism

and among them 2 were having Hashimotos thyroiditis, one of whom had a goiter. All women received Thyroxine in the required dosage.

In Delhi 20% of the pregnant women were documented to have overt hypothyroidism. In few parts of Northern India, the majority of the pregnant women had subclinical cases[16]. In Foreign countries there was about 13% prevalence of overt hypothyroidism. Among the hypothyroid women in UK, 40% of them were having autoimmune thyroiditis.[14] In our country, Anti Thyroperoxidase antibodies were documented in more than 65% of women with hypothyroidism during pregnancy.[44] So in our study we screened 4 infants for the presence of Anti Thyroperoxidase antibodies because hypothyroidism was detected in those women at the time of delivery. The values were within normal range.

A large study on infants born to women who were hypothyroid till parturition may be required to know and to document the transfer of these antibodies to infants and their outcome. Researchers had noticed a free passage of Anti Thyroperoxidase from mother to infants in animal models after passive immunization with recombinant mouse TPO. A study in 2008 at National Institute of Child Health and Human Development showed that infants born to women with autoimmune thyroiditis had 22.7% of sensorineural hearing loss. The rise in antibodies to thyroid occurs mostly during the first trimester of pregnancy and it can pass to the infants through the umbilical cord during parturition.[10]

Infants with congenital hypothyroidism, there will be delay in the developmental mile stones. In abroad studies showed cerebral cortex can be affected in infants born to women whose hypothyroidism corrected during the pregnancy.[47] In our study developmental mile

stones were assessed at 2nd and 4th month of life. All the infants attained social smile at 2months and good head control at 4 months of life.

The infants in our study group showed an average birth weight of 2.5± 0.47 which was less than the control group but was not statistically significant. TSH in all the infants in the study group was normal. Similarly in Western countries there was no significance between the birth weight and hypothyroidism. However in China, they documented an increased incidence of low birth weight among congenital hypothyroidism infants and also popular databases. TSH testing has to be done in infants only after 48hrs, since there can be variations in TSH levels during first 2 days after birth.[48]

Congenital hearing loss is increasing in its incidence. Early detection, treatment and rehabilitation during the growing years can prevent the progression and severity of disability to a greater extent. To improve the outcome of interventions if any, the infants have to be screened before 1 month of age and the initiation of treatment has to be done before 6 months[38]. In our study Otoacoustic emissions were used for hearing screening in 280 infants and were confirmed by Auditory Brain Stem Responses at 1st and 4th month of life.

Among those infants in the study who had positive family history and infants born to women whose hypothyroidism detected during the postpartum period showed a prolongation of the latency period of wave V at 30dBnHL but was not clinically significant. In the study group, 2 infants showed a delayed appearance of wave V replicability. The infant which showed replication of Vth peak at 30dBnHL at the 6th month of life was one among the twins. She was the second twin with a birth weight of 1.2kg and born at 37weeks of

gestation. The second infant which showed replication of Vth peak at 30dBnHL at the 8th month of life was born to lady with Hashimotos thyroiditis at the time of birth.

In 1948 Thomas Gold demonstrated otoacoustic emissions from inner ear and David Kemp in 1978 experimented on it and reported their use. Auditory Brainstem Response recordings were first published by Sohmer and Feinmesser in 1967 and Jewett and Williston interpreted the latencies of the waves in ABR in both adults and infants. Over the last 30years, OAE were used for screening newborn hearing and is confirmed by ABR. These are cost effective, simple and reliable method for screening. However, OAE cannot objectively assess the intensity of hearing loss in infants.[36]

Several studies showed that retrocohlear, cochlear or central hearing pathways can be adversely affected in patients with hypothyroidism[39]. In 1989, it was found that prolongation in the I-III and I-V interpeak latencies in BERA occurs in hypothyroid patients. Some studies found prolongation in all frequency latencies and interpeak latencies can occur in hypothyroidism on BERA and bilateral moderate sensorineural hearing loss occurs in about 40% of the hypothyroid patients. The hearing impairement is more in infants with congenital hypothyroidism due to deletion of gene for dual oxidase, for the formation of the inner ear and low hearing threshold.[37]

Earlier there was lack of screening for hypothyroidism during pregnancy. In view of the risks and complications in both mother and infants due to hypothyroidism WHO insisted for the routine thyroid screening in all pregnant women and TSH is the most sensitive test for the evaluation of thyroid disorders.[41]

In 1997, newborn screening for hearing in infants born to subclinical hypothyroid women showed presence of hearing loss in 25% of the cases. Even the present day, the prevalence of undetected sensorineural hearing loss remains high in infants born to hypothyroid women.[49] Study done in North Thames(England) for the evaluation of hearing loss in infants by OAE and BERA, showed 30% prevalence of hearing loss in these infants at 2nd month of life and 20% in 8th month of life. This reduction in number might be by the correction of congenital hypothyroidism after birth. Studies done in Middle East and Europe showed no statistically significant correlation between congenital hypothyroidism and sensorineural hearing loss in these infants.[50] However in India 2% of the infants with congenital hypothyroidism were found to have sensorineural hearing loss.[39]

In most of the clinical studies hearing impairment was evaluated in infants who had developed congenital hypothyroidism. However there is hardly any studies for the evaluation of hearing in infants born to hypothyroid women which is overt hypothyroidism or hypothyroidism being corrected in the early, late part of pregnancy or during the time of birth.

Our study can initiate a need to evaluate hearing outcome in infants born to women whose hypothyroidism was corrected during pregnancy and those who had a positive family history of hypothyroidism. This is supported by the fact that 2 infants with delay in latencies in ABR but they did not have clinically significant hearing loss.

SUMMARY

VII. SUMMARY

Hypothyroidism is the most common endocrinological disorder in the reproductive age group in the developing countries. The prevalence is more for subclinical hypothyroidism and autoimmune thyroiditis. Studies have proved the transfer of Anti Thyroperoxidase antibodies through the placenta from the mother to the infants at the time of birth causing delay in development of newborns.

Maternal hypothyroidism can cause congenital hypothyroidism in infants. Congenital Hypothyroidism can cause sensorineural hearing loss because it can affect retrocochlear, cochlear and central auditory pathway. The early screening for hypothyroidism and hearing impairment in infants were insisted for early initiation of treatment and rehabilitation.

All the clinical studies were on hearing impairment in congenital hypothyroidism. There are hardly any studies explaining the hearing outcome in infants born to women whose hypothyroidism is corrected during pregnancy and also in subclinical hypothyroidism.

In our study we evaluated hearing in 140 infants born to women with hypothyroidism detected with overt hypothyroidism, hypothyroidism during the early or late part of pregnancy and at the time of birth and compared with hearing in infants born to euthyroid women.

The infants underwent audiological evaluation using Otoacoustic Emissions and Brain stem Evoked Response Audiometry at 1^{st} and 4^{th} month of life. All infants had normal TSH levels. The infants born to women with hypothyroidism showed a lower birth weight than the control group. The infants with family history of hypothyroidism had prolongation

in the latency of replicability of wave V at 30dBnHL in BERA but was not clinically significant. In the study group, 2 infants showed delayed appearance of wave V on BERA. Infant who showed a delayed appearance of wave V at 6th month of life was the second twin with a birth weight of 1.2kg and born at 37weeks of gestation. The other infant showed wave V at 8th month of life. She was born to a lady with Hashimotos thyroiditis and was detected at the time of delivery. Around 50% of the infants born to hypothyroid women showed a prolongation of the latencies of wave V replicability at 30dBnHL in BERA in 1st month of life when compared to control group. However by the 4th month of life it had got corrected. This delay was not statistically significant.

Thus our study showed that, infants born to women whose hypothyroidism was corrected during pregnancy had a delayed response (wave V) on sensitive hearing test like BERA. This could be due to maternal hypothyroidism. However this minor delay on BERA was not statistically significant and it also got corrected by 4th month of life. This correction in hearing could be due to normal levels of thyroid hormones in infants after birth. The subtle deficiency in hearing was subclinical and got corrected because mothers' hypothyroidism was treated in time. Therefore correction of hypothyroidism in pregnant women is important. It is best done in early pregnancy.

CONCLUSION

VIII. CONCLUSION

1. Hypothyroidism during pregnancy is common in Kollar region. However most of these cases are diagnosed and treated adequately before parturition.

2. Hypothyroidism affects the hearing in newborns born to women whose hypothyroidism is corrected during pregnancy and also in those who has a positive family history. However its effect on hearing of the infant was seen to be less and transient when the circulating hormones in the infant are normal. Therefore this subtle deficiency in hearing during the first month of life was only subclinical.

3. The infants born to hypothyroid women have to be screened for delay in developmental milestones as well as hearing impairment.

4. Otoacoustic emissions can only be a screening tool. BERA is more accurate and sensitive in diagnosing hearing impairment in newborns. Therefore BERA should be used to evaluate hearing in all infants born to women who had autoimmune thyroiditis, or whose hypothyroidism was corrected late in pregnancy. BERA must also be done in all infants with low birth weight, premature delivery and those found to have congenital or developmental anomalies.

5. Since this study was only a dissertation, studies with larger sample size would be required with estimation of Anti Thyroperoxidase antibodies soon after birth in infants born to hypothyroid women to document the risk of hearing impairment or the hazard ratio in these infants.

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ANNEXURES

STUDY PROFORMA

Patient Details

Name Of The Patient:.....Age:.....Sex.....
Name Of the Guardian of the infant.....
Hosp No.:..... Date of Enrolment in Study:.....
Date of Admission…….... Date of Discharge……..

HISTORY

1. Family History:

Number of siblings:……

History of familial thyroid disorders……

History of any familial hearing loss……

2. Antenatal History:

- Overt hypothyroidism/Detected during pregnancy:…….
- Symptoms:…….
- Free Triiodothyronine:……
- Free Tetraiodothyronine:……
- Thyroid Stimulating Hormone:…….
- Treatment:……

3. Natal History:

- Term of Gestation:……
- Type of Delivery:……..

4. Postnatal History:

- Birth weight:…….
- APGAR score:……
- History of any ICU admissions(if any specify):……
  ……
- Thyroid stimulating Hormone:…….

5. Developmental History:

- 2months: Social Smile- Attained/Not attained
- 4months: Neck holding-Attained/Not attained

Clinical Examination

General Physical Examination:

- Built: Normal/Moderate/Poor
- Active and alert:……

Vital Parameters:

Pulse:……..…..BP:…….RR:……Temperature:……...

Systemic Examination:

- CVS…….
- Respiratory System:…….
- CNS…….

ENT Examination

Examination of

Ear	Right	Left
Auricle:……..		……
Pre Auricular Region:…….		……
Post Auricular Region……		……..
EAC……		……..
TM:……		……..

Facial Nerve:……

Clinical Evaluation of Hearing:

Otoacoustic Emissions:

1^{ST} :……

4^{TH} :……

Brain Stem Evoked Response Audiometry:

Date: Investigator's Signature :

Place:

INFORMED CONSENT FORM

I have read or have been read to me and understand the purpose of the study, the procedure, otoacoustic emissions, that will be used for hearing assessment in the infants. The risks and benefits associated with my involvement in the study and the nature of information that will be collected and disclosed during the study have been explained.

I have the opportunity to ask my questions regarding various aspects of the study and my questions are answered to my satisfaction.

I understand that I remain free to withdraw from the study at any time and this will not change my future care.

I, the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information for dissertation.

Parents / caretaker's name:

Signature/Thumb impression: DATE:

PATIENT INFORMATION SHEET

STUDY TITLE: Hearing evaluation in infants born to Hypothyroid women.

STUDY LOCATION: R L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

AIM: To assess the involvement of hearing in infants born to Hypothyroid women using otoacoustic emissions.

STUDY DETAILS:

In India, subclinical hypothyroidism is becoming a common endocrinological disorder among reproductive age group ladies. There is not much emphasis on literatures showing assessment of hearing acuity in infants born to hypothyroid women. Studies show relationship between the thyroid hormones and the normal development of inner and middle ear and anti thyroperoxidase antibodies cross the placenta from the mother to the infants. Screening of hearing in infants born to hypothyroid women will be done using otoacoustic emissions.

Please read the following instructions and discuss with your family members. You can ask any question regarding the study. If you agree to participate in the study we will collect information (as per porforma) from you. A detailed clinical history will be taken. Infants will be clinically examined. Blood samples will be collected from women and their infants. Otoacoustic emissions will be done on infants born to hypothyroid women

to assess the hearing and the values will be documented and compared with the infants born to euthyroid mothers.

All information collected from you will be kept confidential and will not be disclosed to any outsider. All information collected will only be used for dissertation and publication purposes. This study has been reviewed by the Institutional Ethics Committee and you are free to contact the member of Institutional Ethics Committee. There is no compulsion to participate in this study. The care you will get will not change if you do not wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

WHO TO CONTACT?

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