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RESEARCH ARTICLE

The Association Of Thyroid Dysfunctions With Infertility In Females.

Dr. N. Malaiarasi and Dr. L. Santhanalakshmi.

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Corresponding Author

Dr.N.Malaiarasi.

Abstract

Introduction:-

Infertility is "the inability of the couple to conceive after one year of regular unprotected intercourse without contraception" **WHO 2000**. A significant fraction of global epidemic is contributed by higher prevalence of infertility with estimates ranging between 18 and 20% in India in any group of people Thus it is recognized as an universal burden influencing the socioeconomical, medical and psychological status of the couples. There exist a number of problems associated with hormonal disorders of female reproductive system and all these disturbances result from **aberrant dysfunction of hypothalamic-pituitary-ovarian axis.**

In humans, fertility is maintained by the hypothalamic-pituitary-gonadal axis which consists of highly coordinated and harmonized connections between them. Disturbances at any point in the axis will result in infertility.

Both partners in relationship contribute to infertility.

Identifiable factors of female infertility are hormonal or endocrinal or ovarian disturbances, tubal factors, non tubal factors and unexplained.

Ovarian dysfunction, the leading cause of infertility is strongly associated with altered hypothalamic-pituitary-thyroid-adreno-gonadal axis, the prevailing hormonal milieu that maintains the fertility in women.

Significant interrelations have been found between thyroid disorders and gonadal functions by a number of authors. Moreover the axes concerned with the regulation of thyroid and gonads, the HPO (hypothalamic-pituitary-ovarian) and HPT (hypothalamic-pituitary-thyroid) show functional linkage between them. And they operate together in an integrated fashion.

Various studies show the influence of thyroid dysfunction on reproductive system as thyroid hormones are considerably essential for normal sexual growth and development. So altered thyroid function will adversely affect the fertility status of both sexes.

Disorders of thyroid gland is more common in females when compared to males. And many studies demonstrate that altered thyroid function has adverse effects on female reproductive system. So assessment of thyroid activity gains considerable importance in the work- up of infertility as its disorders lessen the chances of pregnancy.

Many studies have highlighted that thyroid dysfunction as such may result in infertility as synthesis of female sex hormones – estradiol and progesterone require optimum level of thyroid hormones. Hence for the diagnosis of thyroid disease, estimation of thyroid hormones particularly TSH (thyroid stimulating hormone) becomes essential in the investigation part of infertility. This is because of the increased incidence of compromised thyroid function in infertile females as evidenced by higher incidence of raised serum TSH or anti -thyroperoxidase antibody level. Thus it is evident to have a thorough investigation of all the aspects of hypothalamic-pituitary-thyroid axis.

Some patients have elevated or low serum TSH with normal levels of thyroid hormones exhibiting **subclinical thyroid dysfunction, a more common condition seen in infertile patients**. This subclinical thyroid dysfunction which we often leave uncared can adversely affect ovulation directly or indirectly by causing elevation in prolactin.

Correction of thyroid hormonal dysfunction will result in normal health status, restoration of fertility and normalization of menstrual abnormalities. Hence it is essential to manage thyroid dysfunction particularly subclinical cases, by early identification and treatment as these subgroups of infertile patients pass unrecognized.

Therefore it is **thy important to screen for thyroid abnormalities** among women with infertility because of **its frequent, noteworthy and reversible consequence on infertility.**

Aims And Objectives:-

1. To evaluate and compare the levels of thyroid hormones in the study and control groups.
2. To assess and compare the thyroid stimulating hormone levels between the two groups.
3. To compare the estrogen levels between the study population and controls.
4. To study the impact of thyroid dysfunction on female fertility.

Thyroid Gland:-

In humans, thyroid is an essential endocrine gland. Its main function is to maintain tissue metabolic activity by enhancing oxygen consumption by almost all the cells of the body. It is because of the action of two significant hormones - thyroxine and triiodothyronine, the source being thyroid gland.

The gland starts synthesizing thyroid hormones by 11weeks of intra uterine life. By 20 weeks of gestation, the thyroxine produced by the fetus reaches a significant level whereas the tri iodothyronine levels remains low till 30 weeks of pregnancy after that starts increasing reaching 50 ng/dl at term **Eugster, Erica et al., 2004**.

Physiology Of Thyroid Hormones:-

The thyroid gland secretes **iodothyronines**, which are formed by the union of iodine and tyrosine residues.
In a normal adult the thyroid gland secretes approximately 80µg of T_4 and 6 µg of T_3 per day. About 80% of total production of T_3 arises from peripheral deiodination of T4 and this occurs in peripheral organs primarily in liver and kidneys catalysed by a microsomal enzyme 5'-deiodinase. Various hormones and neurotransmitters regulate deiodination.

Upon secretion, almost entire T_4 and T_3 are tightly bound to serum proteins. A very minimal portion of the entire amount circulates as **free form to enter cells and exert metabolic control**. The binding proteins serve as a protected reservoir to prevent renal clearance.

In serum, the thyroid hormones are bound to three binding proteins thyroid binding globulin (TBG), transthyretin or thyroid binding prealbumin (TBPA) and human serum albumin (HSA).

The plasma levels of binding proteins are increased by estrogens and reduced by androgens and glucocorticoids.

Mechanism Of Action:-

The thyroid hormones execute their functions mainly by its genomic action – activation of nuclear transcription. This leads to enhanced functional activity of all the cells.

The circulating thyroid hormones enter cells by passive diffusion and also via the monocarboxylate 8 (MCT8) transporter and act primarily by binding to nuclear thyroid hormone receptors (TRs) α and β with high affinity thus stimulating gene transcription that bring about the cellular actions.

The receptors have distinctive isoforms. $TR_{\alpha-1}$ is especially expressed in cardiac and skeletal muscle. It is the dominant one that transduces thyroid hormone action on the heart. By contrast, $TR_{\beta-1}$ is expressed more in the brain, liver, and kidneys and its expression is restricted to the pituitary, hypothalamus, cochlea and retina.

T_3-bound $TR_{\beta-2}$ is responsible for inhibiting expression of the prepro-TRH gene in the paraventricular neurons of the hypothalamus and the β subunit TSH gene in pituitary thyrotropes. Thus the negative-feedback effects of thyroid hormone on both TRH and TSH secretion are largely mediated by $TR_{\beta-2}$. The amplified hormonal potency of T_3 than T_4 is attributed to its increased affinity (10–15 times) for thyroid receptor.

An understanding of TR subtypes and tissue expression is important because inactivating mutant genes have increasingly been found to be causes of clinical syndromes manifested by **resistance to thyroid hormone (RTH syndrome),** the most common mutations occuring in the $TR_{\beta-2}$ subtype.

Regulation:-

Three possible regulatory mechanisms of thyroid hormones include:-

- Hypothalamic- pituitary- thyroid axis –involving thyroid releasing hormone from hypothalamus, thyroid stimulating hormone from anterior pituitary and the thyroid hormones.
- Autoregulation - by means of iodide. It has a biphasic action. At relatively low levels of iodide intake, the rate of thyroid hormone synthesis is directly related to the availability of iodide. However, if the intake of iodide exceeds 2 mg/day, the intraglandular concentration of iodide reaches a level that suppresses NADPH oxidase activity and the NIS and TPO genes and thereby the mechanism of hormone biosynthesis. This autoregulatory phenomenon is known as the **Wolff-Chaikoff effect.** As the intrathyroidal iodide level subsequently falls, NIS and TPO genes are derepressed and the production of thyroid hormone returns to normal. Thus constancy of the plasma concentration of thyroid hormones is maintained.
- Regulation by other factors - besides TSH, which is the major regulator of thyroid gland there occurs a wide range of substances viz. insulin-like growth factor I (IGF-I), epidermal growth factor, transforming growth factor (TGF-β), cytokines, ETs –(endothelins) that manipulate thyroid hormone synthesis.

Infertility:-

Infertility, a reversible state in contrast to sterility is the inability to conceive after 12 months of frequent coitus without use of any contraceptives.

In India the data on the prevalence of infertility is sparse with almost none from southern India **Paul C. Adamson 2011.** In developing nations it is seen that one among four couples suffer from infertility **Mascarenhas MN et al.,2012.** This is in concordance with the study conducted by **WHO 2012.**

In India, roughly 13–19 million couples are infertile **ICMR and NAMS 2005.** Evidences cite that most of the Indian states have attained a total fertility rate of < 2.1. This shows a spectacular and an unparalleled reduction in fertility. Thus infertility appears to be a social epidemic besides affecting physical and psychological aspects of mankind.
According to standard protocol **Ferri's Infertility.Clinical Advisor 2014.**, the factors contributing in infertility evaluation include female factors (40%), male factors (40%), the combination of both and unexplained infertility (20%) **Kanal P Sharma et al., 2006**
Hence the major goals in the comprehensive investigations of the infertile couple include

- Identification and correction of factors contributing to the infertile state over a short span of time.
- Providing accurate information, education and counseling to both the partners, explaining the process of reproduction and the nature of therapy.
- Providing counseling about alternatives if pregnancy fails.Fertility gets impaired in thyroid dysfunction especially in hypothyroidism, which causes alteration in the peripheral estrogen metabolism. This decreases the production of sex hormone binding globulin (SHBG) thereby increasing the availability of free sex hormones. They in turn elicit an odd feedback action on the HPT axis.

Gerhard et al.,1991 demonstrated an affirmative relation between various reproductive hormones and basal TSH particularly in the first half of cycle. **Bohnet et al.,1981 considered sub clinical hypothyroidism as an infertility factor itself**

Arojoki et al., 2000 found elevated serum TSH levels in 4% women presenting with infertility for the first time.

Raber et al., 2003 carried out a prospective study by involving a group of infertile women and allowed them to undergo TRH stimulation test and also analysed that SCH was found more common in studies with TRH stimulation test.

Hence it is now recommended that females expecting conception are advised to keep their TSH levels < 2.5μIU/ml. **The Endocrine' Society clinical practice guidelines 2007**

In a study conducted by **Induverma et al., 2012**, of the 394 infertile women enrolled, 94 women were diagnosed as hypothyroid. Based on their TSH values they are categorized into clinical (37.3%) and suclinical (62.7%) hypothyroid groups. Of them, 76.6% became pregnant following thyroxine supplementation (dose depending upon TSH levels). This recommended the maintenance of a normal TSH level as the pre-requiste for fertilization and also justified the choice to commence thyroid supplements in SCH as early as possible.

Thyroid autoimmunity and infertility:-

- AITD, Auto immune thyroid disease – a common disease constituting about 5 to 10% of women in the child bearing age group.
- Commonly, it presents as an isolated condition without affecting thyroid function and so it is often left unnoticed **Bjoro T et al., 2000.**
- **Abalovich et al.,** demonstrated a frequent correlation between endometriosis and AITD.
- **Janssen et al., 2004** observed yet another particular association between this autoimmunity and ovarian disease, particularly PCOS.

Materials And Methods:-

Place Of Study:-

This study a prospective cross sectional study was conducted in the Department of Obstetrics and Gynaecology, Government Rajaji Hospital in co-ordination with the Institute of Physiology, Madurai Medical College, Madurai for a period of one year after obtaining approval from the ethical committee of Government Rajaji Hospital, Madurai.

Sample Size:-

Total subjects - 100
Study population - 50
Controls - 50

Study Population:-

Females attending the Outpatient department of Obstetrics and Gynaecology, Government Rajaji Hospital / Madurai Medical College for primary infertility.

Inclusion Criteria:-

1. Age between 21 – 35 years
2. Duration of marriage: >1 year (following regular and unprotected intercourse)

Exclusion criteria:-

1. Male infertility factor.
2. Amongst the female factors- polycystic ovarian disease, tubal factor, any obvious organic lesion, any congenital abnormality of urogenital system
3. Any history of disease pertaining to thyroid
4. H/o surgery related to thyroid or gonadal system
5. H/o practising any contraceptive measures.
6. H/o intake of drugs such as

- NSAIDs – Meloxicam, Diclofenac and others
- Immunosuppressants – Cyclophosphamide
- Steroids – Prednisolone
- Anti-epileptics – Valproate
- Anti-psychotics – Risperidone, Amisulpride
- Thyroid medications

7. H/o chemotherapy or radiotherapy for malignancy

Control Group:-
Age matched fifty (50) parous women from the general population are allocated to this group.

Materials Used For Stud:-
1. Proforma – to record the anthropometric measurements and the clinical findings of the subjects.
2. Portable weighing machine – to record the body weight in kilograms.
3. Stadiometer – to measure the standing height in centimeters.
4. Standardized mercury sphygmomanometer – to record the Blood Pressure in mm of Hg.

Methodology:-
The study was initiated with the approval of Institutional ethical committee, Madurai Medical College, Madurai and was carried out after explaining the procedures in detail and getting written informed consent from the subjects.
The experimental protocol includes

1) **Recording of a detailed history** including history of hypothyroidism or hyperthyroidism, history of cardiovascular disease, diabetes mellitus, hypertension, surgery or any drug intake and family history of infertility and thyroid disorders.
2) **Measurement of Anthropometric Indices**:
   The subjects were asked to stand erect, with their arms relaxed at their side and feet together.
   The following were measured:
   - **Weight** (in kilograms) was recorded using a portable standard weighing machine.
   - **Height** (in centimeters) was measured to the nearest 0.5 cm using a stadiometer.
   - **Body Mass Index (BMI)** was calculated using Quetelet's Index.
     BMI = Weight (Kg)/ Height (m^2).

1. **Recording of vital signs** viz. pulse rate, respiratory rate and measurement of blood pressure were done and documented.
2. **Blood investigations:** The investigations include
   1. Serum T_3, T_4 and TSH
   2. Serum estrogen – estradiol (E_2) in the follicular phase of menstrual cycle.

For venous blood collection, antecubital vein of front of forearm was selected. Skin was sterilized over the vein with a spirit cotton swab. And about 3 ml of blood was collected in a disposable syringe of 5ml capacity.

For separation of serum, blood taken in a glass tube was first allowed to clot at room temperature and then centrifuged. This separated serum was used to estimate serum T_3, T_4 and TSH and serum oestrogen.

Estimation of thyroid hormones:-

Method:-
Direct solid phase enzyme immunoassay using thyrokit.

Procedure:-

- **50µL of sample and 50µL of control were pipetted into the appointed wells** coated with streptavidin + **50µL** each of **two monoclonal antibodies (**anti T_3, anti-T_4 or anti-TSH of high affinity and specificity) **Horse Radish Peroxidase conjugate** and **Biotin conjugate** were added to all the wells.
- Using orbital shaker the plate was shaken for 10 seconds and then incubated for 1hour for T_3 and T_4 and 2 hours for TSH at room temperature.
- Strips were washed 3 times to eliminate the non reacted species and **100 µL of chromogen Tetra Methyl Benzidine (TMB) substrate** was added into each well and then incubation was done at room temperature for 15 minutes for T_3 and T_4 and 30 minutes for TSH.

- Immunological reaction was stopped by adding **100 µL of stop solution, the sulphuric acid** to each well and the developed colour indicating the absorbance was measured photometrically within 30 minutes with microtiter reader at the wavelength of 450 nm.

Calculation:-

The mean optical densities of standards versus the respective hormone concentration were plotted on semilog graph paper and the concentration of the hormone in the sample was determined by interpolation from calibration curve. As per the thyroid profile, based on the TSH values the study and the control groups are categorized as

- Euthyroid - with the value of TSH between 0.44 – 4.45 µIU/ml
- Hypothyroid - with the value of TSH greater than 4.45 µIU/ml
- Hyperthyroid - with the value of TSH lesser than 0.44 µIU/ml

Estimation of oestrogen:-

Method:-

Quantitative determination of serum estradiol was done in the follicular phase of menstrual cycle by Chemiluminescence immunoassay method (CLIA).

Reference range:-

Phase of menstrual cycle	Range
Follicular Phase	9 – 175 pg/ml
Luteal Phase	44 – 196 pg/ml

Sensitivity: 6.5 pg/ml.

Discussion:-

As per the demographic data, though the population of India is likely to reach two billion by the year 2035, quite majority of them are childless, suffering from infertility **Seshagiri PB et al., 2001**

A report from our country showed that about 13% of women of age group 15-49 years were infertile in 1981 which raised to 16% by 2001 **Palatty et al., 2012.** Thus in India, approximately thirty million pairs endure the pain of infertility.

Endocrines have central role in maintaining fertility and the thyroid hormones are found responsible for normal sexual function.

The thyroid affects every aspect of the gonadal axis. Thus it appears to be a major regulator of reproductive function. It exerts its effects

- by directly acting on ovaries as evidenced by the receptors on oocytes or
- indirectly by decreasing sex hormone binding proteins (SHBG)

Thereby exerting profound effects on reproduction and pregnancy **Rijal B et al., 2011.**

As thyroid disorders have significant and most common association with infertility, it becomes mandatory to assess the thyroid status of both the partners. As the diagnosis of thyroid disorders is quite simple, proper management often reverses its effects on infertility resulting in enhancement of health, regularization of menstrual cycle and restitution of fertility **Trokoudes et al., 2006.**

In this present study, we have analysed the correlation of thyroid dysfunctions in 100 subjects for a period of one year of which 50 were fertile women constituting the control group and the remaining 50 were infertile women constituting the study group in whom the male factor of infertility and the other female factors contributing to infertility like PCOS, tubal causes, any congenital abnormality in the urogenital system and any organic pathology were excluded. Thus subjects with unexplained infertility were included.

In this study, majority of the infertile (35/50; **70%**) and fertile (46/50; **92%**) women had serum T_3, T_4 and TSH within normal range and this is in concordance with study of **Binita Goswamy et al., 2009.**

This study revealed that 30% of our study group had thyroid dysfunction and possibly resulted in infertility. In the control group thyroid dysfunction was found to be 8%.

This present study shows concordance with the study by **Rahman et al., 2008 (33.3%)**. **Sharma et al., 2007** and **B Rajil et al., 2011** studied the frequency of thyroid dysfunction as 23% and 25.6% respectively. Thus it is clear that deranged thyroid levels will affect the fertility status of females. In the present study 70% of the cases were in euthyroid state with the cause of infertility being contributed by other factors.

In this study the major thyroid dysfunction was found to be hypothyroidism with 30% in the infertile women and 6% in the control group, presenting with deranged levels of TSH. A relatively increased occurrence of higher TSH values in those women in this study highlights their inclination towards thyroid paucity or vice-versa **Sharma priyanka et al.,2013.**

Evidences suggest the existence of strong association between subclinical hypothyroidism and disorders pertaining to ovulation **Lincon S R et al., 1999.** Studies conducted by **Bals Pratsch et al.,1997** and **Grassi et al.,2001** revealed the prevalence of subclinical hypothyroidism in infertility to be 25% and 4.6% respectively.

In this study, about 22% of the cases were found to have subclinical hypothyroidism. This highlights the increased prevalence of subclinical hypothyroidism over clinical hypothyroidism in accordance with **Verma I et al., 2012.**

In this study, the mean values of T_3**,** T_4 and TSH in infertile women were 0.961, 81.48 and 4.164 respectively and in controls 1.079, 87.02, 2.46 respectively and it was found that there exists a statistically significant difference with a **p value of 0.002** in relation to the **mean values of TSH** i.e., occurrence of increased TSH levels in infertile women when compared to control group.

Thus it is found that altered thyroid function seems to be a major cause for infertility. These disorders can be dealt effortlessly and fertility can be assured by restoring euthyroid level. Also subtle variations in TSH levels should not be neglected in such infertile females who remain clinically normal **Biradar S M et al., 2012.**

A study with retrospective investigation of the consequences of usual thyroid function screening revealed that concealed thyroid disease was present in 5.1% of the people studied **Mandakini Parihar et al**., They are often left unrecognized. They should be identified and treated earlier as such infertile women may show positive results. And also expensive treatment modalities can be avoided.

Conclusion:-

Present study shows that there occurs an increased **frequency of hypothyroidism** with subclinical thyroid dysfunction being more prevalent than overt hypothyroidism.

As **hypothyroidism,** the major thyroid dysfunction in infertile women has an undiagnosed **impact on fertility, it is essential to include the evaluation of thyroid related hormones in the standard practice of infertility work-up.** Earlier guidelines state "it is unnecessary for such investigations in asymptomatic patients". But recent evidences are clear and cite "all patients with infertility are to be screened for possible thyroid disorders and treated accordingly". This helps in reverting them to the normal status.

Identifying the cases of hypothyroidism especially subclinical hypothyroidism is a clinical challenge. So evaluation of thyroid status in infertile women should be considered routinely with an intention to identify them earlier to get better outcomes by improving the pregnancy rates**.**

In the present hospital based study, the subjects included in the study group were the true representatives of the women suffering from infertility due to hormonal imbalances as all the other reproductive causes were excluded. Such a study group will give more reliable results on the infertility due to hormonal imbalances.

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