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RESEARCH ARTICLE

HYPERPROLACTINEMIA AND ITS COMPARISION WITH HYPOTHYROIDISM IN INFERTILE WOMEN

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Abstract

Introduction : Human infertility is a complex global health problem. It has multiple social consequences which are especially profound for thyroid hormones in infertility with the aim of determining the degree of association of thyroid hormones with hyper prolactinemia in our population.

Materials and method: In this study, we investigated women who were casesof infertility, who attended the Biochemistry Department, RV Metropolis, Bangalore, India, for hormonal evaluations. Thirty fertile women with similar ages were enrolled as the controls. The status of the thyroid dysfunction and the levels of serum prolactin were reviewed in infertile women and in the controls. The serum Prolactin and the thyroid stimulating hormone levels were measured by using Roche reagents in COBAS 8000 Instruments.

Results: In our study, the serum prolactin levels in the infertile group were found to be high as compared to those in the control group and they were highly significant ($p<0.0001$). The serum TSH levels in the infertile group were found to be high, as compared to those of control group and they were highly significant ($p<0.0001$).

Conclusion: It is therefore Concluded that hyperprolactinemia with thyroid dysfunction may be major contributory hormonal factor in infertility among infertile women and as such , estimation of prolactin and thyroid stimulating hormone should be included in the work up for infertile especially those with hyperprolactinemia.

Introduction:-

Infertility is defined as the failure of couple to achieve conception (Regardless of cause) after one year of unprotected and adequately timed intercourse. It could be primary (when a couple has never conceived despite cohabitation and exposure to sexual activity over a period of two years or secondary inferitility (when a couple have achieved a pregnancy previously but regular unprotected sexual intercourse has not resulted in second pregnancy .

Human infertility is a complex problem, which has numerous consequences depending on the society and cultural background, gender, lifestyle, sexual history, of the people it affects. Infertility is a global public health concern this

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is partly due to its complexity in aetiology as well as difficulty in preventing, diagnosing and treating it . Although infertility is considered by some as primarily a woman's problem, men often contribute to and are also affected.

It has been estimated by WHO that 8-12% of couples around the world experience problems in conception. The consequences of childlessness in developing countries range from economic hardship, social stigmatization, violence and even denial of proper burial rites Other consequences include psychological disturbances social stigma and strain on relationships between husbands and wives.

The main causes of female infertility include ovulatory disorders, pelvic inflammatory disease (PID), endometriosis, and polycystic ovarian syndrome, and advanced age, environmental and occupational exposure to chemicals, congenital abnormalities and hormonal imbalance.

Anterior pituitary is one of two lobes that make up pituitary gland, which is a small, pea-sized endocrine gland located at the base of the brain anterior pituitary is responsible for creating and releasing over six different hormones that affect many different bodily processes.

Pituitary gland is made of two lobes: the anterior (front) lobe and posterior (back) lobe. The anterior pituitary creates and releases over six different hormones, which regulate various cellular processes including:

1. Growth.
2. Metabolism
3. Reproduction.
4. Response to stress or trauma.
5. Lactation.

Pituitary gland secretes the following hormones:

1. Adrenocorticotropic hormone (ACTH or Corticotropin).
2. Antidiuretic hormone (ADH, or vasopressin).
3. Follicle-stimulating hormone (FSH).
4. Growth hormone (GH).
5. Luteinizing hormone (LH).
6. Oxytocin.
7. Prolactin.
8. Thyroid-stimulating hormone (TSH)

Prolactin is defined as a pituitary-secreted polypeptide hormone which was named for its stimulatory action on lactation. Its primary function is to enhance breast development during pregnancy and to induce lactation Measurement of prolactin is usually included in the differential work up for female patients who present with amenorrhea, oligomenorrhoea, galactorrhea, or infertility or for male patients who present with sexual dysfunction. However, its secretion is pulsatile; it increases with sleep, stress, pregnancy, and chest wall stimulation or trauma .Hyperprolactinemia is defined as circulating prolactin levels above normal range, which occurs in conditions other than pregnancy and lactation, when physiological hyperprolactinemia occurs. Even in the absence of hyperprolactinaemia, hypothyroidism can contribute to infertility. This is because thyroid hormones are necessary for maximum production of both progesterone and estradiol

Hormonal disorders of female reproductive system is comprised of a number of problems resulting from aberrant dysfunction of hypo-thalamic-pituitary-ovarian axis. These relatively common disorders often lead to infertility. Difficulty to conceive or subfertility constitutes a major psychological burden. Proper evaluation of these disorders involves a multidimensional diagnostic approach, with a pivotal contribution from clinical laboratories (1)

Measurement of prolactin and thyroid hormones, especially thyroid stimulating hormone (TSH), has been considered an important component of infertility work up in women (2)

Hyperprolactinemia adversely affects the fertility potential by impairing pulsatile secretion of GnRH and hence interfering with ovulation (3, 4). This disorder has been implicated in menstrual and ovulatory dysfunctions like amenorrhea, oligomenorrhea, anovulation, inadequate corpus luteal phase and galactorrhea (5, 6). However, many infertile women present with normal menses despite a raised serum prolactin level. Pituitary hormones such as TSH,

prolactin or growth hormone may act synergistically with FSH and LH to enhance the entry of non-growing follicles into the growth phase.

Morphological changes observed in the follicles in hypothyroidism can be a consequence of higher prolactin production that may block both secretion and action of gonadotropins (7). Adequate thyroid supplementation restores prolactin levels as well and normalizes ovulatory function (8).

Thyroid hormones have profound effects on reproduction and pregnancy. Thyroid dysfunction is implicated in a broad spectrum of reproductive disorders, ranging from abnormal sexual development to menstrual irregularities and infertility. [9,10]

Hypothyroidism is associated with increased production of TRH, which stimulates pituitary to secrete TSH and PRL. Hyperprolactinemia adversely affects fertility potential by impairing GnRHPulsality and thereby ovarian function.

Therefore, in every infertile female should be investigated for TSH and PRL levels regardless of their menstrual rhythm at the time of initial consultation. Thyroid hormones have profound effects on reproduction and pregnancy. Thyroid dysfunction is implicated in a broad spectrum of reproductive disorders, ranging from abnormal sexual development to menstrual irregularities and infertility. [9,10]

Infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse.

Infertility affects millions of people of reproductive age worldwide – and has an impact on their families and communities. Estimates suggest that between 48 million couples and 186 million individuals live with infertility globally. (11), (12), (13).

In the female reproductive system, infertility may be caused by a range of abnormalities of the ovaries, uterus, fallopian tubes, and the endocrine system, among others.

Infertility can be primary or secondary. Primary infertility is when a pregnancy has never been achieved by a person, and secondary infertility is when at least one prior pregnancy has been achieved.

Fertility care encompasses the prevention, diagnosis and treatment of infertility. Equal and equitable access to fertility care remains a challenge in most countries; particularly in low and middle-income countries. Fertility care is rarely prioritized in national universal health coverage benefit packages.

The World Health Organization (WHO) performed a large multinational study to determine gender distribution and infertility aetiologies. In 37% of infertile couples, female infertility was the cause; in 35% of couples, both male and female causes were identified; in 8%, there was male factor infertility (14), (15), (16).the most common identifiable factors of female infertility are as follows:

1. Ovulatory disorders - 25%
2. Endometriosis - 15%
3. Pelvic adhesions - 12%
4. Tubal blockage - 11%
5. Other tubal/uterine abnormalities - 11%
6. Hyperprolactinemia - 7%

These factors can contribute to female infertility:

1. Abnormal menstruation.
2. Blocked fallopian tubes.
3. Celiac disease.
4. Kidney disease.
5. Past ectopic (tubal) pregnancy.
6. Pelvic inflammatory disease.
7. Pituitary gland disorders, such as Cushing’s syndrome.

8. Polycystic ovary syndrome (PCOS), ovarian cysts and primary ovarian insufficiency.
9. Sickle cell anaemia.
10. Uterine problems, including endometriosis, uterine fibroids and uterine polyps.
11. Thyroid disease.

Study Design:
This retrospective study was conducted over period of 5 months from 2021 September toJanuary 2022. Over 60 test results were selected in a Regional referral laboratory in Bangalore. The population belongs to Bangalore region.

Investigations:
1. TSH2. prolactin We studied results using TSH and Prolactin different age groups We also studied correlation between TSH level and prolactin in patients.

Methods:-

Analysis of TSH and prolactin Thyroid parameters are commonly measured with the help of Immunoassay (ECLIA) For this study we used e801 modules of Cobas. All modules have same test principle.

Principle of Cobas analyser
Sandwich principle:
1st incubation: serum sample, with a biotinylated monoclonal TSH (or any thyroid parameter) -specific antibody and a monoclonal TSH (or any thyroid parameter) -specific antibody labelled with a ruthenium complex react to form a sandwich complex.)
2nd incubation: Streptavidin coated micro particles are added, which forms an immune complex. This complex gets adhered to solid phase due to interaction of biotin & streptavidin. The reaction mixture is aspirated into the measuring cell where the micro particles get deposited on surface of the electrode. Unbound substances are then removed withProCell/ProCell M. Chemiluminescent emission is induced by electrodes which is measured by a photomultiplier.
Results are determined with the help of 2-point calibration curve.

Reference Ranges:
Reference ranges for thyroid stimulating hormone and prolactin were followed in accordance to
TSH - 0.270-4.20 µIU/ml
Prolactin – 4.79 – 23.3 ng/ml

Statistical Analysis:
Data recording was done in MS Excel. Continuous variables are reported as Mean+ Standard Deviation (SD), Median {Interquartile range (IQR)} and Range.

Shapiro-Wilk test was used to determine whether data sets differed from a normal distribution.

Pearson's correlation coefficient was used to analyse relation between TSH and PRL. For comparison of continues variables between two group unpaired t test was used. All statistical analysis was performed using "R Studio version 1.4.1103". A two-tailed p value of <0.05 was considered to be statistically significant.

Result:-

A total of 30 cases and 30 control with average age of 26.60 years were included in the study with rangeof 20 years to 40 years in cases and 21 years to 40 years for control. (Table 1)

Table 1:- Age Range in cases and control.

	Age		
Group	Mean+SD	Median(IQR)	Range
Case	26.60+4.5908	26.50(22 - 29)	20 – 40
Control	27.7500+4.0615	27.50(25 - 29)	21 – 40

We observed a significant difference (p value=0.0001) for TSH value between Case (6.024+3.9424) and Control (2.483+0.7835). (Table 2)

Table 2:- TSH value in case and control group.

Group	TSH			
	Mean+SD	Median(IQR)	Range	p value
Case *	6.0240+3.9424	5.067(3.0075 – 8.6255)	1.39 – 16.7210	0.0001
Control	2.1483+0.7835	2.03(1.48 – 2.94)	0.69 – 3.39	

*p value 0.0001, statistically significant.

A significant higher PRL value were seen case group (37.3690+13.6681) as compare to the control group (15.1907+3.7830). (Table 3)

Table 3:- PRL value in case and control group.

Group	PRL			
	Mean+SD	Median(IQR)	Range	p value
Case*	37.3690+13.6681	34.50 (26.105 – 45.475)	21.10 – 78.80	0.0001
Control	15.1907+3.7830	14.53(12.70 – 18.70)	6.55 – 21.00	

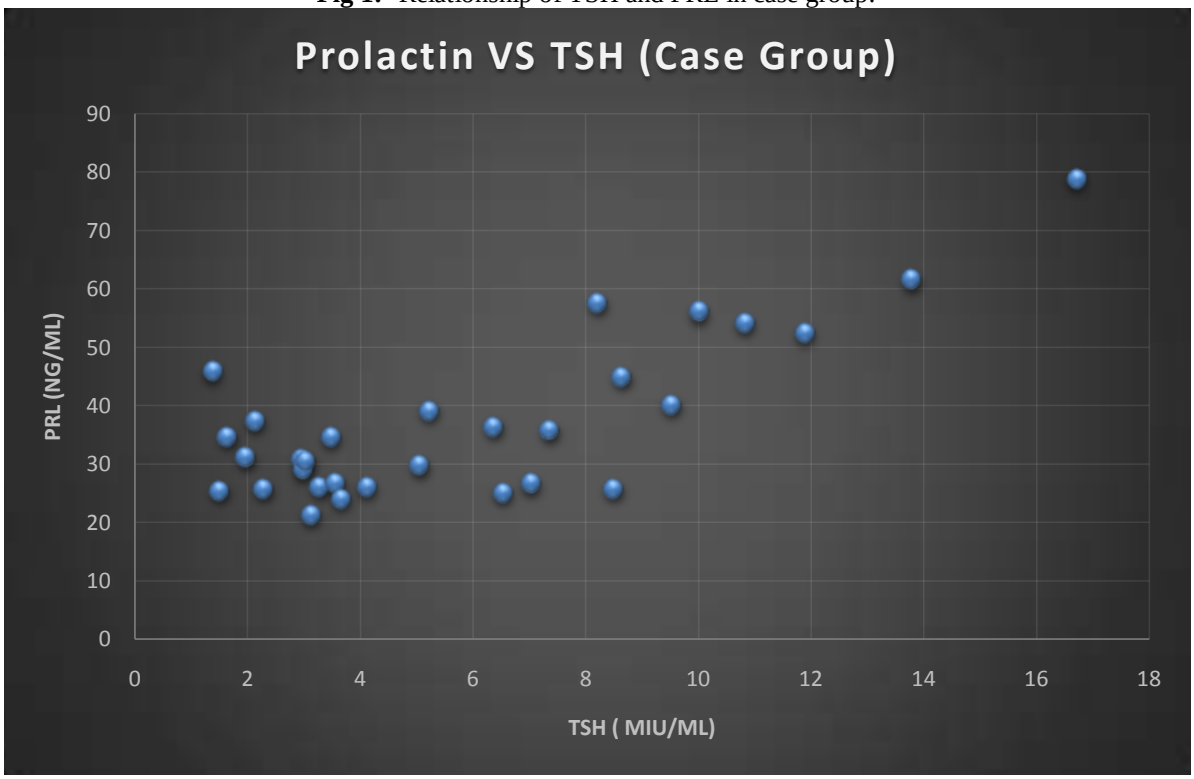
*p value 0.0001, statistically significant.

We observed a strong positive correlation(r=0.7864) between TSH and PRL value in the case group. (Table 4)

Table 4:- Correlation of TSH and PRL in case group.

Cases	Correlation Coefficient (r)	95% CI of r	p value
TSH	0.7864	0.5990 to 0.8921	0.0001
PRL			

Fig 1:- Relationship of TSH and PRL in case group.

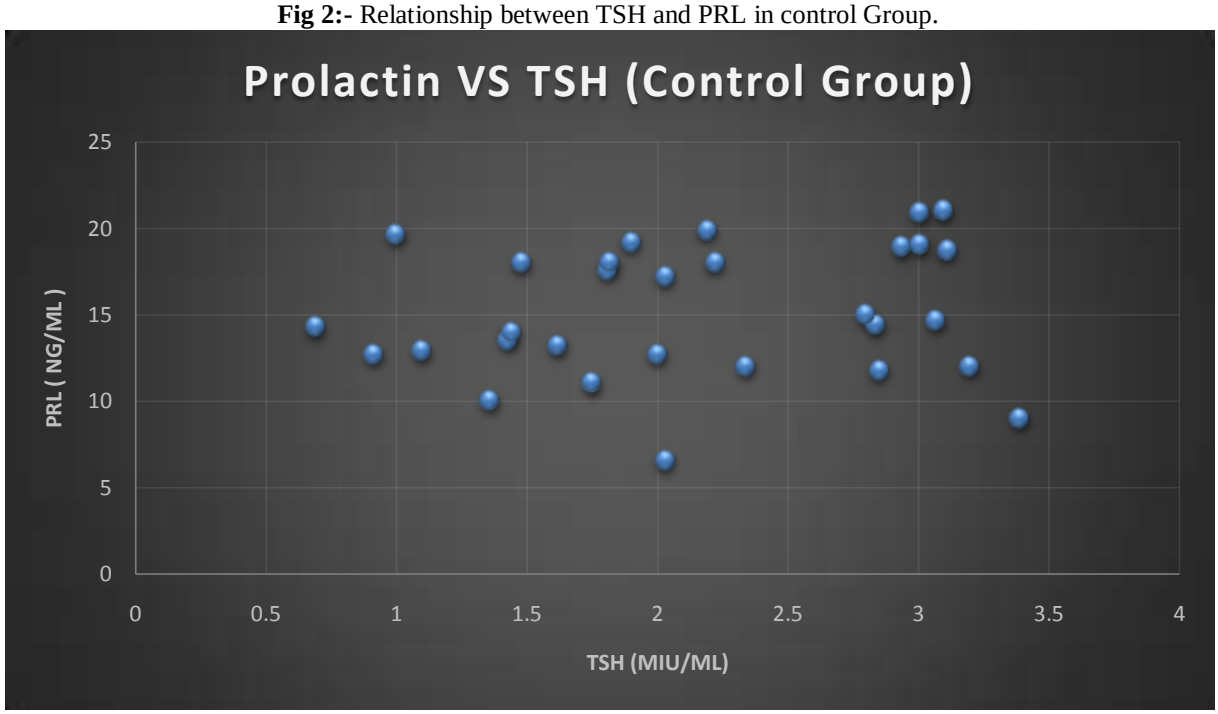


We observed a weak positive correlation between TSH and PRL value in the control group. (Table 5)

Table 5:- Correlation of TSH and PRL in control arm.

Control	Correlation Coefficient (r)	95% CI of r	p value
TSH	0.1442	-0.2279 to 0.4795	0.4472
PRL			

Fig 2:- Relationship between TSH and PRL in control Group.



Discussion:-

Hyperprolactinaemia is a common problem which is encountered in reproductive disorders [17]. The Hyper prolactinemia is not only caused galactorrhoea and amenorrhoea but also gonadal dysfunction and infertility,which led to the need of prolactin estimations. In Our study The serum Prolactin concentration was increased in the infertile group (37.3 ±13.6) as compared to that in the control group (15.1± 3.7) and it was found to be statistically highly significant.

SunithaTurankar et al stated that there was a higher prevalence of hyperprolactinaemia, together with a greater propensity for thyroid disorders in infertile subjects as compared to those in females with normal fertility [18

AffiaTasneem stated that there was a high levels of hyperprolactinaemia, with thyroid disorders in infertile subjects as compared to those in females with normal fertility [19]. In this study stated that some of the women with high prolactin levels had been observed to have hypothyroidism which was characterized by high levels of serum TSH and low levels of T3 and T4.

ArunKoyyada et al stated that There is a significant high prolactin (PRL) level in infertile women with hypothyroidism when compared to euthyroid patients, indicating the relation between hypothyroidism and hyperprolactinemia. The amount of thyrotropin releasing hormone (TRH) from the hypothalamus is markedly increased by inhibition of pyroglutamyl peptidase II, the enzyme catalyzing TRH. The increased TRH in hypothyroidism causes increased thyroid-stimulating hormone and PRL secretion by pituitary, leading to infertility and galactorrhea.(20)

Conclusion:-

There is a correlation of thyroid and prolactin in infertile cases, and this study enabled us to understand one of the most importance of investigating these parameters in infertile cases.

It is therefore concluded that hyperprolactinemia with thyroid dysfunction may be a major contributory hormonal factor in infertility among infertile women and as such, estimation of prolactin and TSH should be included in the workup for infertile women especially those with hyperprolactinaemia.

Reference:-

1.Williams C, Giannopoulos T, Sherriff EA. Investigation of infertility with the emphasis on laboratory testing and with reference to radiological imaging. J ClinPathol. 2003;56:261–7. [PMC free article] [PubMed] [Google Scholar
2. Cramer DW, Sluss PM, Powers RD, McShane P, Ginsburgs ES, Hornstein MD, et al. Serum prolactin and TSH in an in vitro fertilization population: is there a link between fertilization and thyroid function? J Assist Reprod Genet. 2003;20(6):210–5. [PMC free article] [PubMed] [Google Scholar] [Ref list]
3. Poppe K, Velkeniers B. Thyroid disorders in infertile women. Ann Endocrinol (Paris) 2003;64(1):45–50. [PubMed] [Google Scholar] [Ref list]
4 Zollner U, Lanig K, Steck T, Dietl J. Assessment of endocrine status in patients undergoing in-vitro fertilization treatment. Is it necessary? Arch Gynecol Obstet. 2001;265(1):16–20. [PubMed] [Google Scholar] [Ref list]
5.Mishra R, Baveja R, Gupta V. Prolactin level in infertility with menstrual irregularities. J ObstetGynecol India. 2002;52:40–3. [Google Scholar] [Ref list]
6.del Pozo E, Wyss H, Tollis G, Alcañiz J, Campana A, Naftolin F. Prolactin and deficient luteal function. Obstet Gynecol. 1979;53(3):282–6. [PubMed] [Google Scholar] [Ref list]
7Armada-Dias L, Carvalho JJ, Breitenbach MM, Franci CR, Moura EG. Is the infertility in hypothy-roidism mainly due to ovarian or pituitary functional changes? Braz J Med Biol Res. 2001;34(9):1209–15. [PubMed] [Google Scholar] [Ref list]
8.Stoffer SS, McKeel DW, Jr, Randall RV, Laws ER., Jr Pituitary prolactin cell hyperplasia with autonomous prolactin secretion and primary hypothy-roidism. FertilSteril. 1981;36(5):682–5. [PubMed] [Google Scholar] [Ref list]
Bercovici JP. Menstrual irregularities and thyroid diseases. Feuillets de biologie. 2000;74:1063–70.
9. Vaquero E, Lazzarin CD, Valensise H, Moretti C, Ramanini C. Mild thyroid abnormalities and recurrent spontaneous abortion: Diagnostic and therapeutic approach. Am J Rep
10. Mishra R, Baveja R, Gupta V. Prolactin level in infertility with menstrual irregularities. J ObstetGynecol India. 2002;52:40–3. [Google Scholar]
11. GUTTMACHER AF. Factors affecting normal expectancy of conception. J Am Med Assoc. 1956 Jun 30;161(9):855-60. [PubMed]
12.Infertility Workup for the Women's Health Specialist: ACOG Committee Opinion, Number 781. Obstet Gynecol. 2019 Jun;133(6):e377-e384. [PubMed]
13.Recent advances in medically assisted conception. Report of a WHO Scientific Group. World Health Organ Tech Rep Ser. 1992;820:1-111. [PubMed]
14. Mascarenhas MN, Flaxman SR, Boerma T, et al. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med 2012;9(12):e1001356. doi: 10.1371/journal.pmed.1001356 [published Online First: 2012/12/29]
15. Boivin J, Bunting L, Collins JA, et al. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Human reproduction (Oxford, England) 2007;22(6):1506-12. doi: 10.1093/humrep/dem046 [published Online First: 2007/03/23]
16.Rutstein SO, Shah IH. Infecundity infertility and childlessness in developing countries. Geneva: World Health Organization 2004.
17.Choudhary SD, Goswami A. Hyperprolactinemia and reproductive disorders - a profile from north east. J Assoc Physicians India. 1995;43:617–18
18.Hyperprolactinaemia and its Comparision with Hypothyroidism in Primary Infertile Women.,SunitaTurankar , Kanchansonone and AvinashTurankar
19.TasneemAffia, et al. The incidence of hyperprolactinaemia and associated hypothyroidism: local experience from Lahore Centre for Nuclear Medicine, Mayo Hospital Lahore, 2 Government College for Boys Gulberg Lahore. PJNM. 2011;1:49–55.
20.Role of hypothyroidism and associated pathways in pregnancy and infertility : Clinical insights
Arunkoyyada, Prabhakar 2020 oct – Dec ;32 (4) : 312- 317.