

Original Research Article

Response of leuprolide on gonadal functions of women with overt hypothyroidism: a tertiary care centre study from Uttar Pradesh, India

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ABSTRACT

Background: Hypothyroidism can cause menstrual disturbances mainly oligoanovulatory cycles and sometimes menorrhagia. It has also been seen to cause subfertility and pregnancy related complications. Various studies have been done to evaluate gonadal dysfunctions in overt hypothyroidism but very few studies are there which have done using a gonadotrophin response in that subset of patients. Present study evaluates the response of leuprolide on gonadal functions of women with overt hypothyroidism in a tertiary care centre at Meerut.

Methods: In this study 50 females of age 20 to 40 years with newly diagnosed overt hypothyroidism were taken as cases and age and Body Mass Index (BMI) matched healthy females were taken as controls. Both in cases and controls, basal FSH, LH, estradiol was measured on 2nd day to 5th day of menstrual cycle. Thereafter Leuprolide 20 mcg/kg was given subcutaneously on the same day. Post leuprolide test, stimulated LH, FSH and estradiol were measured. Basal and stimulated values were compared between both groups.

Results: Basal LH was significantly higher in controls (8.2 ± 3.2 mIU/L) when compared to cases (6.45 ± 2.75 mIU/L) with a p value $0.03 (< 0.05)$. Basal estradiol and FSH levels were found to be nearly similar and non-significant in cases and controls. No significant differences were found between stimulated mean LH and estradiol in both the groups. Leuprolide response after stimulation test was found to be sluggish in patients with overt hypothyroidism compared to normal euthyroid controls. This study is the rare one done on human subject in tertiary care centre of India, however large sample and multicentric trials are necessary before establishing the biochemical results.

Conclusions: Pituitary and gonadal (ovarian) response to leuprolide was found to have impaired (decreased) in overt hypothyroidism cases. This is the first study to be done in overt hypothyroid subjects to assess both basal and stimulated gonadotropin levels.

Keywords: Hypothalamo pituitary gonadal axis, Hypothyroidism, Leuprolide, Oestradiol

INTRODUCTION

Normal thyroid function is important to maintain normal reproduction, via its interaction in several pathways.¹ Both hyperthyroidism and hypothyroidism are associated with alterations in SHBG and gonadal steroids. In females, thyroid dysfunction has also been linked to reduced fertility and pregnancy complications. In past, studies were done on animal models with overt

hypothyroidism to evaluate hypothalamo-pituitary-gonadal axis, which had shown that in overt hypothyroidism basal gonadotropin levels were normal as in healthy subjects but there was a sluggish response to stimulation with gonadotropin releasing hormone when compared to healthy subjects. It has variety of designations, including mild thyroid failure, as well as compensated early latent, mild, minimally symptomatic, and preclinical hypothyroidism.² The Whickham Survey

and NHANES III.^{3,4} India has estimated 42 million people suffering from thyroid diseases, with prevalence of SCH as high as 9.4 %, with female dominance of 11.4 vs. 6.2% in men.⁵

This study is done to compare basal Follicular Stimulating Hormone (FSH), Luteinizing Hormone (LH) and estradiol (E2) levels between subjects with overt hypothyroidism and euthyroid controls and also to see the response of pituitary ovarian axis to gonadotropin stimulating hormone. The study has been done in subclinical hypothyroidism patients with TSH >10 μ IU/ml to evaluate the effects of overt hypothyroidism on reproductive system.

METHODS

It was an observational case-control study conducted from September 2018 to August 2019 (1-year duration) in Lala Lajpat Rai Memorial Medical College, Meerut. Fifty female subjects within the age group 20 to 40 years, newly diagnosed with hypothyroidism were taken as cases and age and BMI matched euthyroid subjects were enrolled as controls. Only those females whose menstrual cycle ranged between 21 to 35 days with variability of less than 7 days were included in the study. Women having pregnancy or lactation, exposure to chemotherapy or radiotherapy, or having any chronic systemic illness (diabetes mellitus, chronic kidney disease, chronic liver disease, chronic infections, systemic inflammatory disorders, malignancies, congestive heart failure etc.) were excluded from the study.

Subjects having cycle length <21 or >35 days or on drugs affecting the thyroid hormone and gonadal hormone metabolism were also excluded. Patients with TSH >10 μ IU/ml with normal T4 were excluded from the study so that effects of even mild thyroidal failure can be assessed. In all the subjects, Total T4, TSH were measured by CLIA method. Total T4 normal range was taken as 6 - 13 μ g/dl. Subjects with serum TSH >10 μ IU/ml were considered as cases with overt hypothyroidism. And subjects with serum TSH levels 0.5-4.5 μ IU/ml were considered as euthyroid controls.

Both in cases and controls, basal FSH, LH, E2 (estradiol) levels were measured by CLIA method at 8 am in fasting state on 2nd to 5th day of the menstrual cycle. Then Leuprolide subcutaneous injection 20mcg/kg was given to both the groups on the same day. One hour after injection, stimulated LH and E2 levels were measured. Basal values and leuprolide stimulated values were compared between the cases and controls.

Statistical analysis

For statistical analysis the test of significance used was chi square test, p-value <0.05 was considered statistically significant.

RESULTS

Mean age of presentation was found to be 32 yrs. Overall, presentation was with nonspecific complaints. Most common presentation was goiter. 24 out of 50 cases presented with complaint of swelling in front of neck. The next common presentation is as a screening test in view of positive family history despite any symptoms. Basal LH in cases is 6.06 ± 2.10 mIU and in controls it is 6.63 ± 2.38 m IU/ml. Basal LH is significantly more in controls when compared to cases with a p value $0.01 (<0.05)$. Mean levels of stimulated LH in cases was 26.68 ± 8.74 mIU/L and in controls it was found to be 21.62 ± 8.37 mIU/L. No significant difference was seen in leuprolide stimulated LH levels between cases and controls. Mean estradiol levels 1 hr after leuprolide stimulation in controls is 75.48 pg/ml and in cases it is 66.32 pg/ml. No significant difference was found in peak estradiol levels between cases and controls with non-significant p value. Mean increment of LH in cases is 13.73 m IU/ml and in controls it is 14.74 m IU/ml. When increments in LH are compared, no significant difference was found between cases and controls.

DISCUSSION

Studies showed that in overt hypothyroidism basal gonadotropins will be normal but the response to gonadotropin releasing hormone is sluggish, they present with infertility for which cause could not be identified. In this study most common presentation pertaining to thyroid is goiter. The next common presentation is as a screening test in view of positive family history despite any complaints. This highlights the increased awareness among people and clinicians about thyroid dysfunction. In the present study mean basal E2 was found to be non-significant. Compared to controls with p-value >0.05. This suggests that estradiol levels are not affected in moderate to severe degree of hypothyroidism. This study was done in subjects with overt hypothyroidism that would potentially affect the reproductive axis as compared to euthyroid controls. Mean basal LH in cases is 8.2 ± 3.2 mIU/L vs 6.45 ± 2.75 mIU/L in controls with a significant P value of $0.01 (p < 0.05)$. Mean basal FSH is 8.39 ± 3.26 mIU/L vs 7.76 ± 2.90 mIU/L in cases and controls respectively with no significant difference. In a study by Neema Acharya et al, in the subclinical hypothyroid group serum FSH and LH levels were decreased in females who had menorrhagia and infertility.⁶ The conflicting results among these quoted studies and the present study can be explained by different categories of hypothyroidism, presence of autoimmunity, and also variability in presence and severity of symptoms. Mean peak LH in cases is 26.68 ± 8.74 mIU/L and in controls it is 21.62 ± 8.37 mIU/L. There is no significant difference in between cases and controls. Mean peak estradiol (E2) in cases and controls was 66.32 and 75.48 pg/ml respectively with no significant difference. A study was done on "Serum FSH, LH and Prolactin Levels in Women with Thyroid

Disorders” by T Veeresh, D Moulali et al.⁷ The result of this study indicates that there is significant (>0.001) increased basal levels of serum LH as compared to FSH. Thus, the ratio of LH: FSH altered from 1:1 to 6:1. The basal levels of LH are significantly more in controls compared to cases, with no difference in basal FSH and E2. In a study by Sanjay Saran et al, serum E2 (M=50.00; SE=2.25) was low in cases than controls (M=81.48; SE=5.52), respectively.⁸ These differences were statistically significant with a p value <0.05. This study was done in subjects with overt hypothyroidism that would potentially affect the reproductive axis as compared to euthyroid controls. All the above referred studies were done in subjects with overt hypothyroidism except one study by Neema Acharya et al.⁶ In a study done by Larry A Distiller et al, titled “Assessment of pituitary gonadotropin reserve using LHRH in states of altered thyroid function” eight overt hypothyroid patients were evaluated, concluded that in two patients there is an inadequate LH response with normal FSH response, suggesting limited pituitary LH reserve.⁹ Here in present study, basal levels of gonadotropins was evaluated as well as assessed the response of gonadotrophs to leuprolide. Very few studies are done in men. One of these done by Velazquez et al, titled “effect of thyroid status on pituitary gonadotropins and testicular reserve in men” concluded that there is defective LH response to GnRH in hypothyroid men.¹⁰

CONCLUSION

The response of pituitary gonadotrophs to leuprolide is normal in contrast to overt hypothyroidism where the response is sluggish. This is the first human study to be done at tertiary care centre in women with overt hypothyroidism to assess both basal and stimulated gonadotropin levels. Further studies are required in large multicentric trials to confirm these biochemical findings.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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