

Original Research Article

Assessment of gonadal functions in women with subclinical hypothyroidism in Western Uttar Pradesh, India

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ABSTRACT

Background: In females, hypothyroidism can cause menstrual disturbances mainly oligomenorrhea. Thyroid dysfunction has also been linked to reduced fertility and pregnancy complications. Several studies have been done to evaluate gonadal dysfunctions in overt hypothyroidism but very few studies are there regarding subclinical hypothyroidism. Present study evaluates the gonadal functions of women with subclinical hypothyroidism.

Methods: Total 20 females of age 18 to 35 years with newly diagnosed subclinical hypothyroidism were taken as cases and 20 age and body mass index (BMI) matched healthy females were taken as controls. Both in cases and controls, basal FSH, LH, estradiol were measured on 3rd or 4th day of menstrual cycle at 8 AM on fasting. Thereafter Leuprolide 20 mcg/kg was given subcutaneously on the same day. One hour after injection, LH and estradiol were measured. Basal and stimulated values were compared between both groups.

Results: Basal LH was significantly higher in controls (6.63 ± 2.38 m IU/ml) when compared to cases (6.06 ± 2.10 m IU) with a p value 0.01 (<0.05). No significant differences were found between stimulated LH and estradiol in both the groups.

Conclusions: In mild thyroidal failure the response of pituitary gonadotrophs to leuprolide is normal in contrast to overt hypothyroidism where the response is sluggish. This is the first study to be done in subclinical hypothyroid subjects to assess both basal and stimulated gonadotropin levels. Further studies are required in large samples to confirm these findings.

Keywords: Gonadal dysfunction, Subclinical hypothyroidism, Subclinical hypothyroidism and fertility, Thyroid disorders in women

INTRODUCTION

Normal thyroid function is important to maintain normal reproduction, via its interaction in several pathways.¹ dysfunction has also been linked to reduced fertility and pregnancy complications. Previously several studies were done on animal models and in humans with overt hypothyroidism to evaluate hypothalamo-pituitary-gonadal axis. It was 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. SHBG is decreased resulting in low Total E2 and T, but free hormone is normal when compared with euthyroid healthy individuals. But there are very few studies in patients with subclinical hypothyroidism. Subclinical hypothyroidism is a condition of mild to moderate thyroid failure defined biochemically by normal levels of thyroid hormones with mildly elevated TSH concentrations.² It has variety of designations, including mild thyroid failure, as well as compensated, early latent, mild, minimally symptomatic,

and preclinical hypothyroidism.³ Expert panel has divided SCH into two categories : i) mild elevation of TSH (4.5-10 m IU/L) and ii) more severe elevation of TSH (>10 m IU/L).⁴ Prevalence of SCH has been reported to be between 4 - 10 % of general population according to two large population based studies, The Wickham Survey, and NHANES III.^{5,6} 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.⁷

This study is done to compare basal follicular stimulating hormone (FSH), luteinizing hormone(LH) and estradiol(E2) levels between subjects with subclinical 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 4.5 - 10 µ IU/ml to evaluate the effects of even mild thyroid failure 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. Twenty female subjects within the age group 18 to 35 years, newly diagnosed with subclinical hypothyroidism were taken as cases and twenty 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 3 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 5 - 12 µg/dl. Subjects with serum TSH 4.5 - 10 µ IU/ml were considered as cases with subclinical 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 3rd or 4th 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 SPSS software v 21 was used. 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 27 yrs. Overall, presentation was with nonspecific complaints. Most common presentation was goiter. 8 out of 20 cases presented with complaint of swelling in front of neck. Mean levels of stimulated LH in cases was 20.37±10.32 m IU/ml and in controls it was found to be 20.802±8.67 m IU/ml (Figure 1).

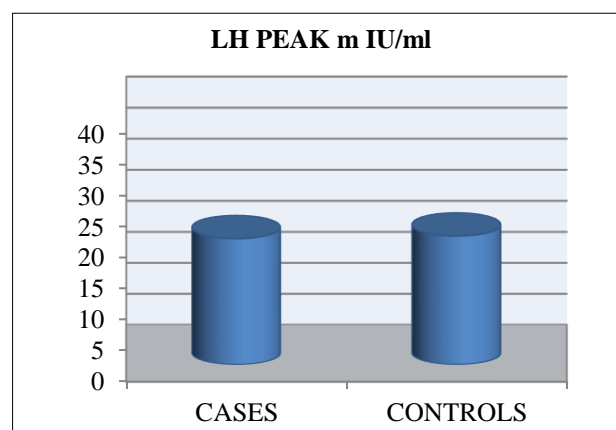


Figure 1: Mean peak LH levels in cases and controls.

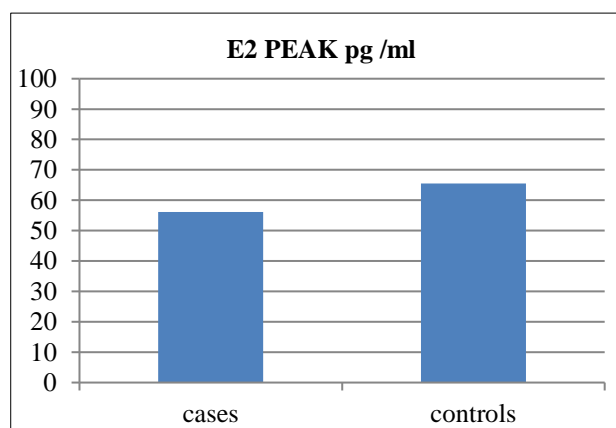


Figure 2: Mean peak estradiol in cases and controls.

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 65.54 pg/ml and in cases it is 56.12 pg/ml (Figure 2). 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 (Figure 3). When increments in LH are compared, no significant difference was found between cases and controls.

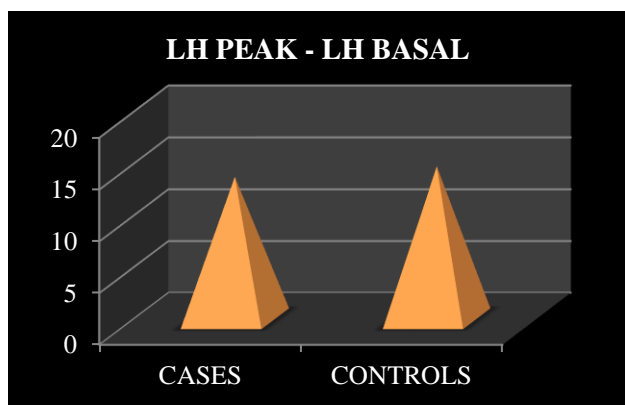


Figure 3: Mean increment in LH after leuprolide injection in cases and controls.

DISCUSSION

Studies showed that in overt hypothyroidism basal gonadotropins will be normal but the response to gonadotropin releasing hormone is sluggish. Very few studies are done in subclinical hypothyroidism. Subclinical hypothyroid (SCH) subjects may have normal menstrual cycles, but they present with infertility for which cause could not be identified. This study was done in SCH subjects having TSH 4.5-10 μ IU/ml with normal menstrual cycles. Main idea behind this is to find out the sole effects of SCH on HPO axis excluding the effects of other disorders affecting the reproductive system and also to know the effects of even mild thyroid failure on HPO axis. Subclinical hypothyroid subjects are those who presented or referred to endocrinology OPD with nonspecific symptoms. 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 44.16 vs 55.37 in cases and controls respectively with $p > 0.05$ which is non-significant. This suggests that estradiol levels are not affected in mild degree of thyroidal failure. 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. In the present study only SCH subjects with mild thyroid dysfunction were taken. So, the difference may not be obtained.

Mean basal LH in cases is 6.06 ± 2.01 mIU/L vs 6.63 ± 2.38 m IU/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.⁹ 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. Levels after leuprolide stimulation: Mean Peak LH in cases is 20.37 ± 10.32 m IU/ml and in controls it is 20.80 ± 8.67 m IU/ml. There is no significant difference in between cases and controls. Mean peak E2 in cases and controls was 56.12 and 65.54 pg/ml respectively with no significant difference. When Increment of LH is compared i.e., LH peak - LH basal mean value is 13.73 Vs 14.74 in cases and controls respectively, with no significant difference. This is the first study in subclinical hypothyroidism done to assess the pituitary ovarian axis to leuprolide stimulation. One of the previous studies done by Larry A Distiller et al, titled "Assessment of pituitary gonadotropin reserve using LHRH in states of altered thyroid function" 8 overt hypothyroid patients were evaluated, concluded that in 2 patients there is an inadequate LH response with normal FSH response, suggesting limited pituitary LH reserve.¹⁰ 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.¹¹ But this is not observed in subjects with mild hypothyroidism in the present study, suggesting that this mild degree of thyroid dysfunction will not affect pituitary gonadotrophs responsiveness to GnRH. A study was done on "Serum FSH, LH and Prolactin Levels in Women with Thyroid Disorders" by T Veeresh, D Moulali et al. 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, and also there is significant (>0.001) increase in serum prolactin levels in hypothyroidism.¹² They concluded that the alteration in menstrual cycle and decreased reproductive performance of women are similar to polycystic ovarian disease and can be explained on the basis of altered hormone profile of LH, FSH and prolactin. Increased levels of prolactin and LH with normal FSH in hypothyroid cases was seen, indicating their susceptibility for the development of polycystic ovarian syndrome. So, the basal levels of LH are significantly more in controls compared to cases, with no difference in basal FSH and E2. On leuprolide stimulation there is no difference in peak LH and E2 between cases and controls. All the above referred studies were done in subjects with overt hypothyroidism except one study by Neema Acharya et al. Here in present study, author evaluated basal levels of gonadotropins as well as assessed the response of gonadotrophs to leuprolide. So, this is the first study to assess the response of gonadotrophs to leuprolide in subclinical hypothyroidism.

Main limitations of this study are small sample size. Also, etiology of subclinical hypothyroidism was not

assessed (autoimmunity) and prolactin levels were not measured which can be affected in hypothyroidism and prolactin can affect the reproductive system.

CONCLUSION

It can be thus be concluded that in mild thyroidal failure the response of pituitary gonadotrophs to leuprolide is normal in contrast to overt hypothyroidism where the response is sluggish. This is the first study to be done in SCH subjects to assess both basal and stimulated gonadotropin levels. Further studies are required in large samples to confirm these findings.

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Conflict of interest: None declared

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

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