ASSOCIATION OF THYROID HORMONE LEVELS WITH LUTEAL PHASE DEFICIENCY IN INFERTILE WOMEN

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ABSTRACT

Objectives: To find out the association of thyroid hormone levels with Luteal Phase Deficiency (LPD)

Methodology: This prospective study was conducted at Peshawar Medical College, from April to August 2013. The sample size was 125 infertile women of the reproductive age group (18-42 years) selected through consecutive sampling technique. On the 22nd and 23rd of the menstrual cycle, endometrial biopsies were performed. Chemiluminescence Immunoassay was used to estimate the serum levels of the thyroid hormones. SPSS version 19 was used to conduct the statistical analysis. The Chi-square test was used to see whether there was any statistically significant difference between the endometrial findings of patients with normal thyroid profiles and those who had elevated thyroid hormone levels. It was deemed statistically significant when the probability value was $p<0.05$.

Results: The majority of infertile patients (n=99) had normal thyroid profiles, followed by hyperthyroid cases (n=23). Only three turned out to be hypothyroid. There was no significant difference in endometrium between the patients with normal and increased thyroid hormone levels.

Conclusion: Although no statistically significant association between the thyroid hormones levels and the endometrium in cases of Luteal Phase Deficiency could be found in this study, their role cannot be ignored and needs further evaluation

Keywords: Infertility; Endometrium; Thyroid Hormones; Luteal Phase Deficiency.

INTRODUCTION

For implantation of a fetus, adequate preparation of the endometrium is mandatory. The hormone responsible for this is progesterone, produced by the corpus luteum after ovulation. Logically, any derangements in progesterone production should lead to infertility. One such condition of insufficient progesterone exposure is luteal phase deficiency (LPD).[1] It is defined as endometrial histology inconsistent with the chronological date of the menstrual cycle. The endometrium lag behind 2-3 days from the menstrual cycle date. As a result, the luteal phase is reduced to less than 12 days duration (minimum of 13 days from the duration of LH surge or 11 days of elevated body temperature).[2] LPD is implicated as one of the factors contributing to infertility and or recurrent early pregnancy loss.[3] In one of the studies, carried out in the United States, LPD has been found in 10% of infertile patients.[4] Another study in India showed it to be present in 20% of infertile patients.[5] However, occasionally LPD is found in normal menstruating and fertile women.[6] This observation led to the notion that along with LPD, some other factors are also involved in the causation of infertility.

The exact etiology and pathogenesis of LPD are not clear. It is thought to be caused either by deficient progesterone secretion by the corpus luteum or unresponsive endometrium to normal levels of progesterone. Corpus luteum arises from the dominant follicle, the development of which is dependent on Follicle-stimulating Hormone (FSH) secretion. Any imbalance in FSH production will affect normal folliculogenesis. The other hypothesis focuses on the Luteinizing (LH) Hormone. Women with LPD maintain a fixed pattern of increased LH rather than an acceleration in phase frequency with the approach of ovulation. The unresponsiveness of endometrium may be due to abnormal progesterone receptor concentrations or failure to express certain adhesion molecules.[4]

Besides hormones of the hypothalamic-pituitary-gonadal axis, other hormones that are involved in pathogenesis are prolactin and thyroid hormones. Association of abnormal thyroid hormone levels with menstrual irregularities have long been implicated.[7] Hypothyroidism is particularly thought to be associated with LPD, either through secondary hyperprolactinemia or alteration in sex hormone binding levels.[4] Another

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suggested mechanism is that hypothyroidism reduces the size of ovarian follicles.[8] There is not much literature available on hyperthyroidism; however, it is clear that it affects estradiol metabolism and alters gonadotrophin secretion.[9]

Diagnosis of LPD remains an area of controversy. The endometrial biopsy is currently the best approach to determine LP because it demonstrates changes necessary for the implantation of the embryo.[2,10] The other tests are measuring serum progesterone levels, Basal body temperature (BBT,) and sonographic findings. Progesterone levels fluctuate during 24 hours (from 2.3 to 40.1 pg/ml), making its measurement difficult.[11] BBT rises with the rise of progesterone in the post-ovulatory period. The problem with BBT measurement is that it lacks specificity and sensitivity.[4] Furthermore, normal fertile women can have abnormal BBT.[2] Sonography is not recommended as a standard test due to problems of interobserver variability and lack of clinical expertise.[4] Therefore, we designed this study to find out whether thyroid hormone levels affect endometrial morphology and dating. The objective of this study is to find out the association of thyroid hormone levels with LPD in infertile women.

METHODOLOGY

This prospective cross-sectional study was conducted in Peshawar Medical College, Peshawar from 21st April 2013 to 10th August 2013 by the approval of Institutional Review Board of Peshawar Medical College (Ref No. Prime/IRB/2019-189). The sample size was 125 infertile women of reproductive age (18-42years), selected through consecutive sampling technique. In this study, all those patients were included who went through diagnostic laparoscopy for infertility in Health Care Centre during the said period. Patients having a normal assessment of ovulation, a hysterosalpingogram, and semen analysis of spouse were selected for laparoscopy. Their Endometrial Biopsies (22-23rd day of the menstrual cycle) and blood samples were collected after taking the written informed consent. Patients with organic causes of e.g., fibroids, congenital abnormalities of the female genital tract or abnormal semen analysis of their spouses, or who couldn't remember their last menstrual period (LMP) were excluded.

The endometrial biopsies were fixed in 10% buffered formalin and embedded in paraffin. Five microns thick sections were obtained from each paraffin block. The sections were then stained with Hemotoxylin and eosin for histopathological evaluation. The endometrium lag behind 3 days from the date of menstrual cycle was considered LPD. Two consultant histopathologists evaluated the biopsies for establishment of diagnosis.

The blood samples were collected using the aseptic techniques and sent to Madina Medical Laboratory for measurement of serum Thyroid Hormones levels. Chemiluminescence Immunoassay Analyzer CLIA-IIS was used for measurement of serum levels of TSH, T3 and T4. The reference values for thyroid hormones status were taken as TSH (0.35 to 5.3 µl/mL), T4 (5.0 to 13.0 µg/dL), T3 (0.8 to 1.9 ng/mL).

Statistical Analysis was performed using SPSS version 19 statistical program. While calculating p values we excluded hypothyroid patients, because of their low number in this study. Chi Square test was used to evaluate the morphological differences in endometrial tissue biopsies of patients with normal thyroid hormone levels and increased thyroid hormone levels. Probability value $p \leq 0.05$ was considered statistically significant.

RESULTS

In our study, 125 infertile patients were included. The mean age in this study was 28.13± 5.11 years. The mean duration of infertility was 7.13 years. 57% patients had primary infertility while 43% had secondary infertility. 99 out of 125 infertile patients (79.2%) had normal thyroid profiles, followed by hyperthyroid cases n=23 (18.4%). Only 3 (2.4%) turned out to be hypothyroid. Frequency of LPD in infertile females with

Table 1: Luteal phase deficiency in normal and hyperthyroid females

Endometrium	Hyperthyroid	Euthyroid	Total (%)
Coinciding with LMP	10	45	55 (45.08)
Lag by 3-4 days	6	33	39 (31.97)
Lag by 5-6 days	3	13	16 (13.11)
Lag by 7 or > 7 days	4	8	12 (9.8)
Total	23	99	122 (100)

Table 2: Association of luteal phase deficiency with thyroid hormone status

Thyroid status	Lagging	Coinciding	Total	P Value
Hyperthyroid	13	10	23	0.86
Euthyroid	54	45	99	
Total	67	55	122	

normal and abnormal thyroid hormone levels are shown in Table 1.

The endometrium was coinciding with dates in 55 (45%) of women. Out of these 55, majority of females (n=45, 82%) were euthyroid, while only (n=10, 18%) were hyperthyroid. LPD was found in (n=67, 55%) of patients on endometrial biopsy. Out of these 67, majority (n=54, 81%) of these women were euthyroid, while only (n=23, 19%) were hyperthyroid.

Table 2 shows association of LPD with thyroid hormone status. There was no significant difference in endometrium between the patients with normal and abnormal thyroid hormones levels.

DISCUSSION

In our study, we assessed endometrial biopsy of 125 female infertile patients. LPD was found in 55% of patients. Majority (81%) of these women were euthyroid, while only (19%) were hyperthyroid. There was no significant difference in endometrium between the patients with normal and increased thyroid hormones levels.

LPD has been the subject of debate for decades. Its etiology is still not clear. The current study was carried out to find if thyroid hormones had some role in its causation, as they control general metabolism.

The mean age in this study is 28.13 yrs which is in accordance with study conducted by Rehana et al[12] and Neelofar et al[13] at Peshawar and Karachi respectively. While mean age of infertile women calculated by Paul et al[14] in India is slightly lower than this study i-e 25.9 years. The study by Kasius et al[15] in Netherlands shows a higher value than ours i-e 32 years. The difference may be due to early marriages in the Indian sub-continent.

The mean duration of infertility is 7.13 years in our study which is similar to other studies conducted by Shamsunnisa et al[16] and Tanveer et al[17] i.e. 6 years and 5 years respectively. But the study conducted by Sujata et al[18] and Kasius et al[15] show mean duration of infertility of 2.2 years and 3.5 years respectively. The increase in duration in our cases could be due to delay in seeking medical advice.

In our study, 57% patients had primary infertility while 43% had secondary infertility. This is in accordance with study done by Shamsunnisa et al[16] which showed 61% patients had primary infertility and 39% had secondary infertility. Study from India showed 82.2% of patient having primary infertility and 17.8% with secondary infertility.[19]

In present study, majority of infertile women had normal thyroid profiles (79.2%). Other studies also show similar results.[20-22] Among patients with thyroid hormonal abnormality, only three (2.4%) turned out to be hypothyroid while 23 (18.4%) were hyperthyroid. This finding is contrary to study done by Elahi et al in Pakistan[20], Goswami et al[22] and Santosh et al[23] in India. However, there are studies in favor of our findings. Studies carried out in Pakistan by Lalani et al[24] and in India by Kameswaramma et al[21] showed that hyperthyroidism is more prevalent in infertile females. In fact, both hypo and hyperthyroidism can lead to infertility. The high frequency of hyperthyroidism as compared to hypothyroidism in our study may be due to the fact that hyperthyroidism is much prevalent in our region.[25,26] There is limited number of studies available on effects of hyperthyroidism on fertility.[9]

LPD was found in 55% of infertile patients. A similar study done in our country showed LPD to be 60%.[27] A Nigerian study showed 12.8% of infertile patients had LPD.[28] Another study carried out in India by Girish et al showed 20% of infertile patients had LPD.[19] Though our study shows high rates of LPD, majority of our patients shows lag by 3-4 days, while study by Girisch et al revealed majority had lag by 5-6 days. Anyhow, LPD is much prevalent in our region. In addition, sufficient work has not been done on this aspect of infertility. We also correlated thyroid hormones status with LPD, and p value turned out to be insignificant. This means, that some other factors may be responsible for LPD in infertile patients. Although one cannot ignore the role of thyroid hormones, as endometrium do express thyroid hormone receptors.[29] After thorough literature search with available resources, we could find only one article which showed positive effect of thyroid extract on infertile women with LPD.[30]

We recommend studies including large sample sizes to explore the potential role of Thyroid hormones in causing LPD and subsequent infertility. Serum Antithyroid antibodies should also be included in the evaluation of such patients, as they may cause such a subtle deficiency in thyroid hormones that do not affect the euthyroid state of patient, but still can lead to subfertility.

CONCLUSION

Although we couldn't find statistically significant correlation between effects of thyroid hormones on endometrium in cases of LPD in this study, we cannot ignore their role and it needs further evaluation.

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Author's Contribution

SN conceived the idea and checked methodology of the study. SZ contributed in writing the original draft. SA and HK helped in writing, reviewing and editing of the manuscript. MMK Supervision. SA supervised the study. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Authors declared no conflict of interest

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None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.