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Relationship of Endometriosis with Cortisol and Thyroid Function in Young Working Females

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ABSTRACT

Objective: The study was focused to evaluate the role of endometriosis in development of hypothyroidism in working females subjected to chronic stress. **Study Design:** Cross sectional study. **Settings:** This research was conducted at department of Gynecology & Obstetrics, The University of Lahore Teaching Hospital, Lahore Pakistan. **Duration:** The research was completed in from February 2023 to February 2024. **Methods:** Serum samples of fifty-five endometriosis patients and fifteen controls were analyzed for T3, T4, TSH, cortisol and estrogen levels by using ELISA kits. **Results:** The levels of TSH in patient's serum is (1.02±0.168mIU/L) as related to control (3.08±1.090 mIU/L) were lower in females with endometriosis. Serum estrogen levels in endometriosis patients (67.07±5.54 pg/ml) were higher than normal controls (21.07±3.66pg/ml). Elevated levels of serum cortisol (27.25±3.27) than normal values (11.19±4.18) in endometriosis patients were observed. Thyroid problems may result from this imbalance. Furthermore, there is a change in the quantity of thyroid hormones (T3 and T4) in endometriotic cells. Production of T4 rose whereas that of T3 fell. Thus, our research shows that endometriosis increases the risk of thyroid malfunction and hormone imbalance in women. **Conclusion:** Endometriosis may play a major role in the development of hypothyroidism in females of reproductive age. The serum thyroid hormone and estrogen levels showed variability among healthy subjects and patients of endometriosis.

Keywords: *Thyroid hormones, Endometriosis, Hypothyroidism, Estrogen.*

INTRODUCTION

Endometriosis is a multifactorial, benign, estrogen-dependent gynecological condition, affecting women through their reproductive years. This disease occurs in 10-15% of women having age ranging from 25 to 35 years.[1,2]

Endometriosis is characterized by the growth of endometrial tissues outside the uterus on ovaries and fallopian tubes. In extreme conditions the tissue grows on bladder, kidneys, intestines and rectum and cause infertility and pelvic pain. Endometriosis-related infertility is still one of the most challenging complications for the gynecologist.[3] Endometriosis can grow extensively like cancer.[4] The hormonal receptors present on endometriotic lesions and normal endometrium are different from each other. Endometriosis implants show resistance to hormonal treatments, compared to normal endometrial tissues.[5]

High level of chronic stress is linked to endometriosis. The chronic stress correlates with severity of pain and disease. By managing chronic stress, the risk of developing endometriosis may be reduced. In rodents, chronic, uncontrolled stress, either prior to or following experimental endometriosis development, stimulates disease pathways and speeds up lesion progression. Moreover, endometriosis patients are more susceptible to various immune-related and inflammatory disorders, many of which have also been linked to stress. Here, we examine the most recent research on the connection between endometriosis and chronic stress, as well as any

potential reciprocal aspects of this link. If endometriosis is found to be a cause or result of stress, then more research may be needed to determine whether stress-reduction techniques work to lessen symptoms and delay the growth of endometriotic lesions.[6]

Estrogen hormone supports endometriosis lesions to grow and exist, it also promotes the infection, inflammation and pain associated with endometriosis. Endometriosis lesions can also lead to production of their own estrogen because of greater number of (estrogen receptor β) ERβ receptors on endometriosis implants.[7] Estrogen develops the cellular proliferation by the over production of cytokines.[8] Estrogen enhances the production of Prostaglandin E2, which encourages the progression and growth of tumor and also stimulates the action of aromatase, in this way generating a vicious circle which additionally favors the continuous production of estrogen in endometriosis.[7,9]

Diet affects the estrogen levels as diet rich in fibers eliminates the excess of estrogen and drops it's the bioavailability of estrogen, decreasing the chances of endometriosis.[10]

Furthermore, diet rich in fat also rises the levels of estrone, estrone sulphate and estradiol in premenopausal women.[11] Excess production of estrogen inhibits the progesterone receptor on endometriotic stromal cell and decreases the number of progesterone receptors in endometriosis implants.[7]

Thyroid hormones controls body's metabolism. T3 and T4 are two different types of hormones produced by thyroid gland. These hormones play main role in regulating body metabolism. Thyroid gland has a major role in endocrine system – this system integrates all the hormones secreted by the glands in different parts of the body and act as chemical messengers among all the body functions. At times, the thyroid dysfunction leads to increase or decrease secretion of hormones. This imbalance of T3 and T4 become the reason of complications during menstrual cycle, difficulty in conception and with intrauterine fetal growth.[12] One out of eight women develops thyroid disease during her lifetime. The occurrence of thyroid disease is more in women with endometriosis. Endometriosis and thyroid dysfunction in combination may increase the intensity of chronic pain and increase endometriosis severity. It is essential to comprehend the relationship between the two so we can have a discussion to improve the health.[13]

Moreover, there is alteration in the growth of endometriotic cells and in secretion of the thyroid hormones (T3 and T4). The production of thyroxine (T4) was high and T3 was decreased. This imbalanced production of T3 and T4 hormones results in thyroid dysfunction. This means that altered levels of thyroid hormones may be associated with endometriotsis.[14,15]

METHODS

This was a cross-sectional study evaluated and supported by Research and Ethics Committee vide letter No. REC-OUL-223-03-2024 at Institute of Molecular Biology and Biotechnology, The University of Lahore. Sample of total seventy was taken out of which Fifty-five (55) working females from 25-30 years of age, suffering from endometriosis, was selected and screened at Jinnah Hospital Lahore. Fifteen (15) out of seventy, age-matched controls were also examined in the current study. The questionnaire was designed to take the consent and medical history. Five ml (5ml) of venous blood sample was taken in gel tube from patients and controls. The sample was then centrifuged within two hours at 4000 rpm. After the centrifugation, the serum was aliquots and stored at -70^{o}C for the examination. Inclusion criteria include the patients suffering from stage IV of endometriosis. Controls were females with no history of endometriosis or associated symptoms. Serum thyroxin (µg/dl), serum triiodothyronine (µg/dl) and thyroid stimulating hormone (mIU/L) was estimated by using human ELISA kit (Bio Vendor). Estradiol (pg/ml) level of each participant was evaluated by ELISA assay (human diagnostics). Cortisol (µg/dL) was assessed by using a human Elisa Kit (Abcam).

Statistical analysis was performed by using SPSS (v.20). Independent T-test and Pearson correlation was applied. All the results were stated in the form of Mean ± SD, whereas, $p<0.05$ was considered significant results.

RESULTS

The data assembled verified that levels of estrogen and thyroid hormones have a major role in the pathogenesis and progression of endometriosis in the female reproductive phase. In table 1, the thyroid profile of young females with endometriosis shows a varied picture between healthy subjects and patients of endometriosis. Higher serum thyroxine (T4) 19.27±3.28 ug/dl Vs 7.98±2.18 ug/dl; $p<0.0061$ was detected in patients of endometriosis against control subjects. Further, the levels of Serum Triiodothyronine (T3) and Thyroid stimulating hormone (TSH) were altered significantly as declining trends were detected in female with endometriosis 60.48±6.24 ug/dl and 1.02±0.168 mIU/L; $p<0.05$ in contrast to controls 121.57±8.24 ug/dl and 3.08±1.09 mIU/L. Highly significant $p=0.0013$ increased levels of serum estrogen 67.07±5.54 pg/ml was evident in patients of endometriosis in comparison to control subjects 21.07±3.66 pg/ml. Likewise, the mean value of serum cortisol 27.25±3.27 µg/dL Vs 11.19±4.18 µg/dL, $p=0.03$.

was statistically significantly increased in females with endometriosis as compared control females.

Table 1: Hormonal profile of controls and patients of endometriosis

Variables	Control (n=15)	Subjects (n=55)	(P<0.05)
Serum thyroxine (T4) ug/dl	7.98±2.18	19.27±3.28	0.0061
Serum Triiodothyronine (T3) ug/dl	121.58±8.24	60.48±6.24	0.0325
Thyroid stimulating hormone (TSH) mIU/L	3.08±1.09	1.02±0.168	0.0057
Estradiol (pg/ml)	21.07±3.66	67.07±5.54	0.0013
Cortisol (µg/dL)	11.19±4.18	27.25±3.27	0.03

Figure 1: Lower TSH in endometriosis patients as compared to controls

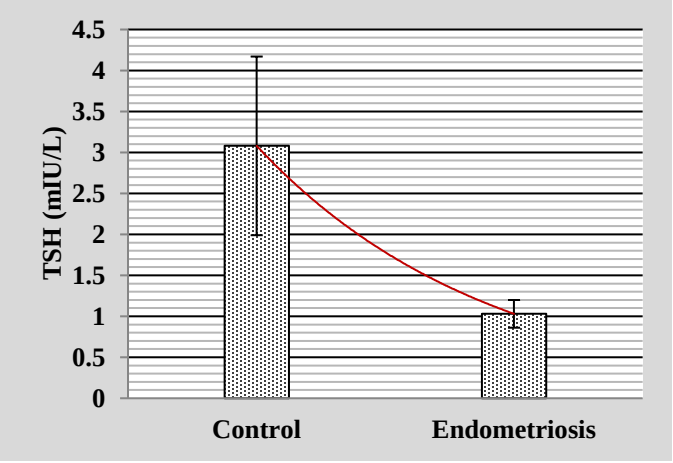
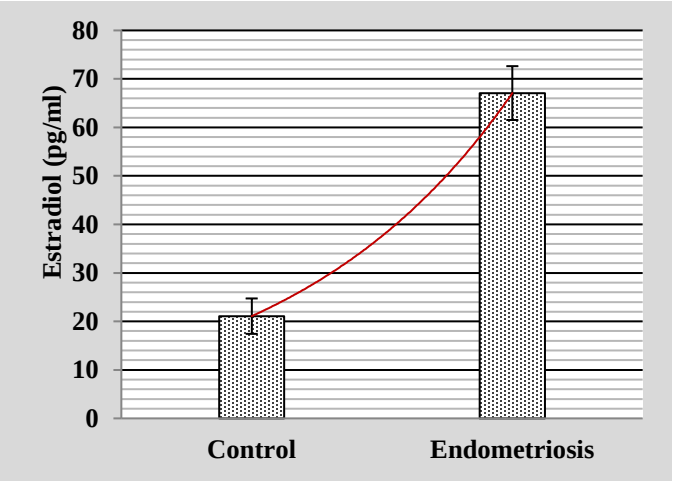


Figure 2: High levels of Estradiol in endometriosis patients



DISCUSSION

Considering the details mentioned above, the study's outcomes explain solid proof of a correlation between endometriosis and thyroid dysfunction. Researchers indicated, "In humans, thyroid dysfunction is related to severe forms of endometriosis".[13] The occurrence of endometriosis appears to be more in working females related to stress.[14] Stress significantly alters numerous immunological factors plus cells including their functions.[15]

Though, endometriosis may react differently to circulating thyroid hormones. Such as endometriosis implants may have altered estrogen and progesterone receptors, which transformed thyroid metabolism.[16] This transformed metabolism can lead to decrease in T3, also causes the resistance to triiodothyronine (T3) action and local increase in production of thyroxine (T4), which results in spread of the endometriosis tissue outside the uterus.[17]

Women with endometriosis are at higher risk of hypothyroidism.[18] Elevated cortisol levels cause the liver's 5-dehydrogenase enzymes to become inactive. This is because they produce inflammatory cytokines such TNF-α, IL-1, and IL-6, which decrease the liver's ability to convert T4 into T3.[19]

Stressful lifestyles, diets lacking in vitamin D, and high levels of estradiol all contribute to elevated cortisol levels in young, working women with endometriosis by boosting the liver's production of Cortisol binding globulin. Because cortisol decreases the body's ability to eliminate estradiol, its levels rise. Elevated cortisol levels inhibit the liver's 5′-deiodinase activity, preventing the conversion of thyroid (T4) and triiodothyronine (T3). The synthesis of inflammatory cytokines as a result of elevated cortisol production inhibits the hypothalamic pituitary thyroid (HPT) axis.[20]

The liver produces more thyroid binding globulin (TBG) as a result of excess of estradiol. The increased sialic acid content and more complex oligosaccharides in this TBG cause structural changes that lengthen its half-life in blood. Thyroid function results from the delayed delivery of T4 to the target tissue caused by the binding of this TBG with T4.[21]

While in few researches there was no statistically significant variation in the levels of thyroid-stimulating hormone between the groups. It was discovered that the endometriosis group's mean T4 value was substantially lower than that of the control group. Thyroid problems and endometriosis were found to coexist in a small number of patients. In addition, there was no statistically significant variation between the groups concerning hypothyroidism and thyroid dysfunction (p>0.05). The

coexistence of autoimmune disorders may be taken into consideration in the follow-up of endometriosis patients if the impact of autoimmunity is apparent in the etiopathogenesis of the condition.[22]

Stress can significantly alter several bodily functions, including hormone and immune system functions. Stress, whether physical or emotional, modifies women's hormone systems, causing an excess of cortisol to be released, which inhibits the body's natural killer cells from activating. When under stress, NK cells are more vulnerable to the deleterious consequences of excessive cortisol production. One of the constant indicators of stress-induced reduction of cell immunity is the decreased activity of NK cells. Emotional or physical stress triggers the release of corticotropin-releasing hormone, which raises cortisol levels in the plasma.[22]

Endometriosis Foundation of America found after an extended period of study that women undergoing endometriosis also have high prevalence of hypothyroidism, fibromyalgia and chronic fatigue syndrome. Moreover, endometriosis has been characterized as an "autoimmune syndrome".[17]

CONCLUSION

In endometriosis patients, the increased half-life of TBG hinders the delivery of T4 to the target region. The liver's capacity to remove estrogen is hampered by cortisol secretion, which could be a reason for high estrogen levels in endometriosis, particularly in women who work in stressful conditions. On the other hand, high cortisol levels inhibit the liver's capacity to convert T4 into T3 by inactivating the 5-dehydrogenase enzymes, thereby causing thyroid dysfunction in endometriotic females.

LIMITATIONS

A cross-sectional study including only 70 female participants was conducted. A bigger sample size, however, can improve the legitimacy of the results and allow for the elaboration of more findings.

SUGGESTIONS / RECOMMENDATIONS

In order to prevent infertility in young working females, further large-scale investigations on this area are advised.

CONFLICT OF INTEREST / DISCLOSURE

The authors state that there are no conflicts of interest that might be interpreted as compromising the study's declared objectivity.

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