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INSINUATION OF THYROID PROFILE AND INFERTILITY IN YOUNG FEMALES WITH ENDOMETRIOSIS

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ABSTRACT

Endometriosis is a chronic inflammatory disorder characterized by the presence of endometrial tissues and glands which are located outside the uterus such as ovaries and peritoneal cavity. Females suffering from endometriosis often present with infertility. Aim of current study was to assess the thyroid profile in infertile women suffering from endometriosis. Current study was carried out in 50 females with clinically diagnosed endometriosis and 50 controls. Serum level of thyroid peroxidase antibodies (IU/Ml), Serum thyroxin (µg/dl), serum triiodothyronine (µg/dl), thyroid stimulating hormone (µg/dl), progesterone (ng/ml) and estradiol (pg/ml) was evaluated by commercially available human ELISA kit. Thyroid profile demonstrates their vibrant effect among disease group and normal individuals. Higher levels of TPO and T4 (61.65±7.19 IU/MI and 18.65±2.19 µg/dl) were recorded in patients with endometriosis than that of controls (27.29±4.52 IU/MI and 8.31±1.56 µg/dl) whereas the level of T3 (µg/dl) and TSH (µg/dl) was decreased significantly (p=0.032 and p=0.000). Current study concludes that thyroid profile may

stimulate the progression and development of endometriosis. Proper control of thyroid profile may help to prevent endometriosis.

Keyword: Endometriosis, ELISA, thyroid, endometrial tissues, endometriosis

INTRODUCTION

Infertility is the inability to conceive within one year of unprotected intercourse with regular menstrual cycles [1]. The causes can be related to males, females, both (male and female) or in some cases both are normal and the cause is unknown. One of the diseases linked to female infertility is endometriosis which is a pelvic inflammatory syndrome [2]. It is characterized by the presence of endometrial tissues and glands which are located outside the uterus such as ovaries and peritoneal cavity. The abnormal presence of these tissues provokes inflammation resulting in ectopic lesions [3]. In Obstetrics and Gynecology, endometriosis is a commonly encountered chronic inflammatory disease in women. It affects almost 10% of women in the child bearing age [4]. Patients suffering from endometriosis commonly present with painful menstruation, dyspareunia, constant pelvic pain which is chronic in nature and is often associated with infertility [5]. As the endometriosis is linked to infertility and it is never reported before menarche and after menopause, it is often associated with excessive estrogen levels [6, 7]. Thyroid hormones have also been known to interfere with the reproductive system. Whether autoimmunity or the levels of thyroid hormones is the main culprit in various diseases linked to infertility is yet to be determined [8, 9]. The exact aetiology of endometriosis is not known however many theories have been proposed till date. Sampson in 1927 proposed that the backflow of the menstrual blood leads to the implantation and growth of the endometrial tissues and glands in places other then uterus resulting in chronic inflammation. The retrograde menstrual blood regurgitation in the abdominal cavity leads to the implantation of the endometrial cells and development of ectopic lesions. This theory is still the most widely accepted of all the theories proposed for the aetiology of endometriosis [10]. However, it is now known that almost all women during the child bearing age suffer from retrograde menstruation and only some of them develop endometriosis. This backflow of menstruation resulting in endometriosis alone, has failed to justify the etiology [11].

The endometriotic lesions resulting from the retrograde menstrual flow are, metaplastic in nature or have a lymphovascular origin, is still controversial. Immune modulation along with immune cells acquisition and recruitment, mucosal apoptosis regulation by modulations in the paracrine and endocrine systems, all factors combine to play role in endometriosis etiology [12].

Autoimmunity has also been thought to play a major causative role among other suggested causative factors like endocrine and epigenetic modifications [13, 14]. The endometrium is sloughed off by the fallopian tubes into the peritoneal cavity during menstruation. This tissue is cleared from the peritoneal cavity by the immune system. Altered immune system in endometriosis is backed by many studies. Dysregulations in the removal of the endometrial tissue leads to implantation and growth of lesions [15]. Enormous evidence on estrogen modulation of innate and adaptive immunity is present [16, 17, 18]. Estrogen not only regulates number of neutrophils and their functions, it also modulates the release of chemokines and cytokines. Leukocytes were studied in ectopic lesions of the patients suffering from endometriosis, increased estrogen receptors and enhanced expression of anti-apoptotic gene BCL-2 was seen along with densely populated leukocytes [19]. Hence, the retrograde refluxed cells generate cytokines which are immunosuppressive, chemotactic and angiogenic, by irritating the peritoneum [20]. Presence of autoantibodies in endometriosis strongly suggests the role of autoimmunity as a causative factor. Various autoimmune responses like, activation of the B lymphocytes, abnormalities in T lymphocytes, the involvement of multiple organs and familial disposition, all fit the autoimmune disease criteria.

Many studies suggest the association of endometriosis with other autoimmune disorders like rheumatoid arthritis, systemic lupus erythematosus and autoimmune thyroiditis [21]. Number of non organ specific antibodies have also been found in endometriosis [22]. Thyroid peroxidase antibody levels have found to be raised in patients of endometriosis suggesting association with auto immune thyroid diseases [23]. Many studies showed the presence of hypothyroidism in women with endometriosis [23, 24]. This cross sectional study is aimed to determine whether women suffering from endometriosis have thyroid dysfunction or

if they are at higher risk of developing autoimmune disease of thyroid. The current study also tries to establish if the thyroid autoimmunity, which in turn is attributable to raised estrogen levels, is a risk factor for infertility in patients with endometriosis or not.

MATERIALS AND METHODS

Current study was designed to analyse the crucial role of thyroid profile in young infertile females with newly diagnosed endometriosis. Study population encompasses 50 healthy individuals and 50 infertile females of age 25-48 years, suffering from endometriosis was screened at University of Lahore teaching hospital. History of patients was taken at predesigned performa after taking an informed consent. Appropriate laboratory and intensive examinations of endometriotic females and control ones were done prudently. Clinically diagnosed 50 infertile females with endometriosis and 50 apparently healthy subjects were met the criteria for inclusion in the study. Protocols used in present study were ethically approved by "Research and Ethics Committee" at Institute of Molecular Biology and Biotechnology, The University of Lahore, Lahore, Pakistan. Clinically diagnosed stage IV endometriotic patients were added and those with the history of alcohol consumption, cigarette, metabolic dysfunction (Hypertension, Cancer, and diabetes), depression and malnutrition syndrome and on medication including Parkinson or antipsychotic were excluded. From the antecubital vein of study population 5ml of blood sample was drawn. Sample was centrifuged at 4000 rpm within two hours of sample collection. After the centrifugation serum was separated and stored at -70ºC until assayed.

For the estimation of thyroid peroxidase antibodies (IU/Ml), Serum thyroxin (µg/dl), serum triiodothyronine (µg/dl) and thyroid stimulating hormone (µg/dl) human ELISA kit (Bio Vendor) was used. Progesterone (ng/ml) and Estradiol (pg/ml) level of each participant was determined by ELISA assay (human diagnostics).

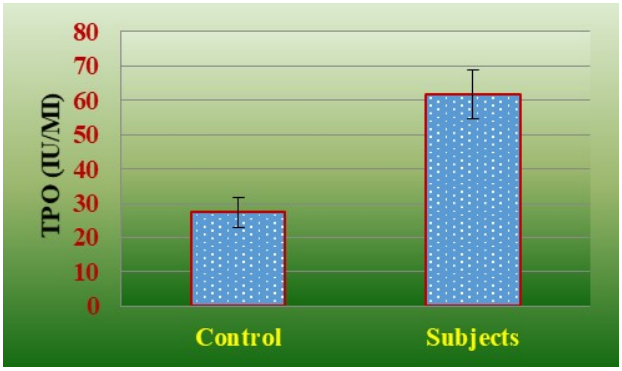
RESULTS

Present study demonstrated that thyroid profile of young infertile female suffering from endometriosis have potential role in disease pathogenesis, aggravation and development. The level of thyroid peroxidase antibodies (TPO) (IU/MI), serum thyroxin (T4) (µg/dl) and serum triiodothyronine (T3) (µg/dl) differed

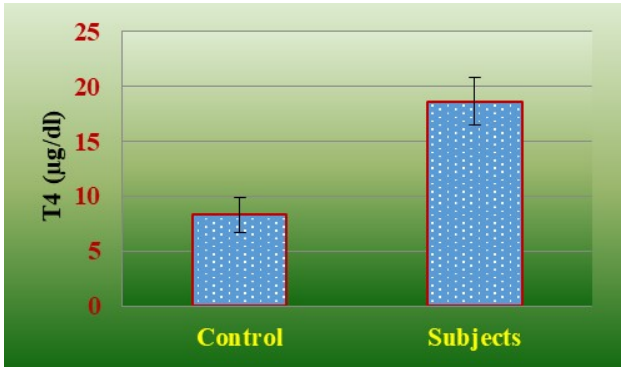
significantly (p=0.031, p=0.021 and p=0.032) with increased level of TPO and T4 (61.65±7.19 and 18.65±2.19) in female suffering from endometriosis as compared to control (27.29±4.52 and 8.31±1.56). Whereas the level of T3 was reduced (62.64±4.18) in diseased group as compared to healthy individuals (107.26±3.47). Decrease level of TSH (µg/dl) and progesterone (ng/ml) was recorded (1.01±0.095 and 8.19±2.42) in diseased subject as compared to control one (3.56±1.06 and 21.62±4.16). As for as the level of estradiol (pg/ml) concerned, significantly (p=0.021) increased level was observed (61.52±3.19) in female with endometriosis than that of healthy females (25.46±3.45).

Table 1: Thyroid profile of young females suffering from endometriosis

VARIABLES	Control(n=50)	Subjects (n=50)	(P<0.05)
Thyroid peroxidase antibodies (TPO) IU/Ml	27.29±4.52	61.65±7.19	0.031
Serum thyroxin (T4) µg/dl	8.31±1.56	18.65±2.19	0.021
Serum Triiodothyronine (T3) µg/dl	107.26±3.47	62.64±4.18	0.032
Thyroid stimulating hormone (TSH) µg/dl	3.56±1.06	1.01±0.095	0.000
Progesterone (ng/ml)	21.62±4.16	8.19±2.42	0.015
Estradiol (pg/ml)	25.46±3.45	61.52±3.19	0.021



(a)



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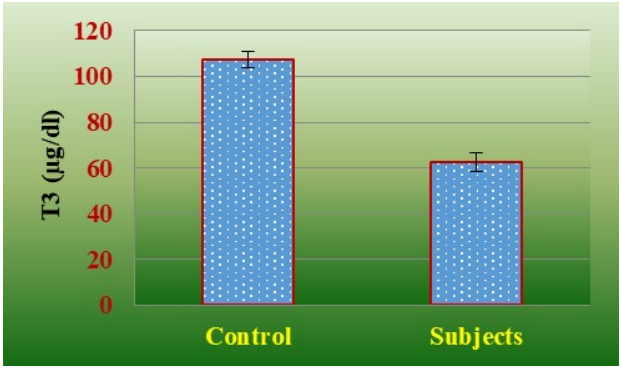

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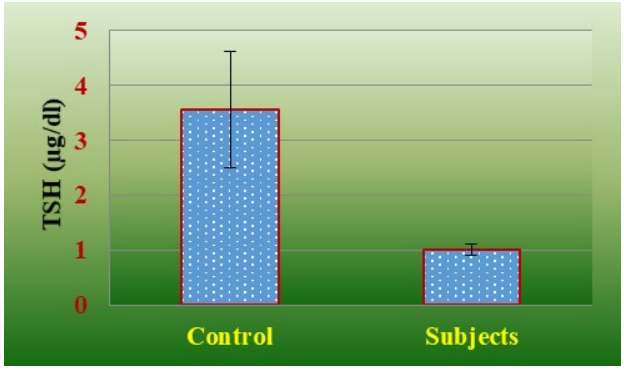

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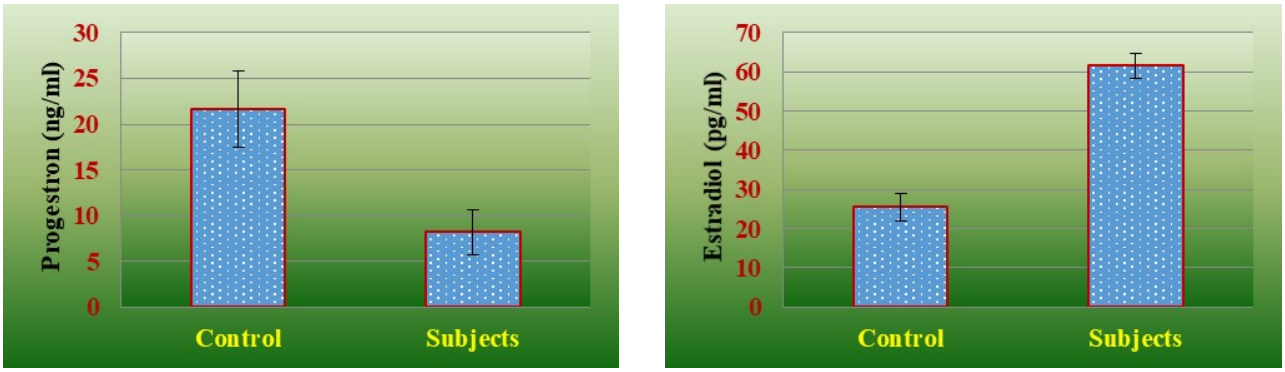

Figure 1: Thyroid Profile Of Young Females Suffering From Infertility and Endometriosis

DISSCUSSION

Autoimmunity and increased estrogen levels both are thought to be very important links between endometriosis and Graves' disease. Individuals who suffer from Graves' disease have hyperthyroidism, dermopathies, goiter and exhibit ophthalmopathies. Grave's disease is an autoimmune disorder in which autoantibodies are found which stimulate the secretion of thyroid hormone and cause enlargement of the thyroid gland. They are also responsible for the dermopathies and the ophthalmopathies [25]. Endometriosis is marked by chronic inflammation and it fits into the criteria of autoimmune disease as it shows the features of altered immune response. The multi colonial activation of B lymphocytes along with the dysfunctioning T and B cells and tissue damage caused by the chronic inflammation. All of these features highlight the presence of autoimmunity in the endometriosis patients [26]. The current study found a significant relation between women of child bearing age suffering from infertility and endometriosis with deranged thyroid function as compared to the women in the healthy control group.

Sinnaii *et al*., 2002, also found that hypothyroidism and incidence of other autoimmune diseases increases if the patient has endometriosis and a strong co-relation exists [27]. The antinuclear antibodies (ANAs) are significantly raised in the patients of endometriosis and Graves' disease as compared to the healthy controls, shown in many studies, strongly suggesting the presence of autoantibodies in both the diseases [26]. Significantly raised reactivity of the antibody named thyroid peroxidase (TPO) antibody has been also seen in the patients suffering from endometriosis as well as Graves' disease Taylor *et al*., 1991) [28]. In one study, thyroid function was investigated in

infertile women, TPO antibodies were raised in infertile women 18% compared to 8% healthy controls. However, among all the causes of infertility, the incidence of TPO antibody was the highest (29%) in endometriosis. Also both hyperthyroidism and hypothyroidism were more prevalent along with raised TPO in women suffering from endometriosis as cause of infertility [29]. The present study shows significantly raised levels of TPO in the endometriosis patients along with deranged thyroid profile. Another study showed that infertile women who had TPO antibodies also had endometriosis (44%) [24]. The current study however shows different findings from a previous study where Petta *et al*., 2007 demonstrated no significant relationship between thyroid dysfunction and endometriosis, according to their results female patients suffering from endometriosis do not possess risk for thyroid diseases [30]. The reason behind this can be their diagnostic criteria for Grave's disease as the TSH receptor antibodies are more specific than thyroid peroxidase antibodies. However, the current study also has numerous limitations. The mean age of diagnosis of endometriosis is 25-35 years [31, 32] whereas for Graves disease average age at diagnosis is around 46-48 years [33]. The present study being a cross sectional study requires additional longitudinal and cohort studies so that the significance of the association can be thoroughly verified. Other confounders also need to be considered are socio economic status and location of the endometriosis. In conclusion, present study demonstrates a strong incidence of endometriosis and thyroid dysfunction in infertile women with TPO antibodies, when compared to the healthy controls.

Many epidemiological studies have shown that women are more affected by the autoimmune diseases during their fertility period [34]. Graves' disease is also 5 times more prevalent in women compared to the opposite gender. The increased prevalence in women is connected to the autoimmune dysfunction frequency in the women compared to males and also to the fact that thyroid hormones interact with estrogen [25]. The fact that normal thyroid function is crucial for the reproductive system is extensively studied [35]. Sex hormones play an important role in the autoimmune response both by paracrine and endocrine means. Sex hormones exert local effects in tissues, where they are synthesized, mainly by cell proliferations and cytokine release.

They effect the apoptosis as well as chemo taxis in a complex manner [36]. Endometriosis has not been reported before menarche or after menopause linking this chronic inflammatory disease to the sex hormones related autoimmunity. The very important link between the patients of endometriosis and thyroid dysfunction is autoimmunity. Estrogens are thought to be immunity response enhancers and progesterone as to be immune suppressor [37, 38]. In many autoimmune diseases like Rheumatoid arthritis (RA), Systemic Lupus Erythematosus (SLE) low levels of androgens and low androgen to estrogen ratio has been detected. The raised estrogen levels modulate the release of pro inflammatory cytokines from the macrophages in various ways. Estrogen is believed to increase the release of inflammatory cytokines from activated monocytes and macrophages. Estradiol exerts proliferative effects on cells and increases the differentiation of monocytes into activated macrophages [38]. Macrophages have a receptor CD-16 which binds to the antibody IgG. Estrogen modulates the expression of CD-16 and modifies the release of inflammatory cytokines TNFα, IL-1 and IL-6 [39]. In a recent study, it was shown that estradiol enhances the secretion of the inflammatory Tumor necrosis factor (TNFα). TNF α through NF-k B inhibits apoptosis and promotes cell proliferation and survival [40].

The cytokines released from macrophages increase the peripheral conversion of androgens to estradiol, resulting in low levels of androgens and high levels of estradiol through the activation of enzyme aromatase [41, 42]. In patients with SLE and RA increased activity of aromatase has been seen [43, 44]. This is in accordance to the findings of the current study where the levels of estradiol are significantly raised in the infertile women with endometriosis. Also the progesterone levels are markedly low in the infertile patients compared to healthy controls. In a recent study it has been shown that increased estrogen metabolites, resulting from the increased hydroxylation in the peripheral tissues by the increased activity of aromatases, result in increased activation of T cells and differentiation of B cells. These differentiated B cells are thus responsible for the release of antibodies [45]. Estradiol has been found to enhance the production of antibodies IgG and IgM. This results in raised levels of anti-ds DNA Ig G [44]. Estradiol has been

found to strongly corelate with inflammation [44]. The estradiol activation of estrogen receptor (ER) results in anti-apoptosis of endometrial cells [46]. It is evident in the natural menstrual cycles that estrogen levels result in proliferation of endometrium and inhibits apoptosis [47]. In vitro, estradiol has shown to increase the cell viability of endometrium [48]. Estrogen has nuclear and extra nuclear means for its anti-apoptotic effects. It increases the transcription of the BCL-2 gene through the nuclear pathway. The extra nuclear pathway is when several kinases (Akt, ERK) are phosphorylated by the estrogen-ER complex [46]. Phosphorylated ERK can only be isolated from the endometrial cells suggesting abnormal response of endometrial cells to estradiol and possess resistance to apoptosis [49]. Akt phosphorylation also promotes cell survival in endometrial cells [50]. Increased Akt activation in endometrial cells is by the overstimulation of ER by estradiol which is synthesized in peripheral tissues by the aromatases [51]. In a recent study anti-apoptotic (truncated) isoform of SRC-1 (steroid receptor coactivator) was isolated from endometriosis which is generated by the cleavage of full length SRC-1, by the matrix metalloproteinase 9 which is in turn activated by the natural killer cells and TNFα [52]. The truncated isoform SRC-1 activates procaspase 8 and hence stops apoptosis [53]. The effects of progesterone are opposite to that of estradiol as it induces apoptosis in endometrial cell culture through inhibition of BCL-2 and NF-k B. This nuclear factor is thought to be the major player in the signalling of the endometrial cell survival [54, 55, 56]. Endometrial cells show resistance to progesterone and hence escape apoptosis [57, 58].

Thus, it can be concluded that apoptosis is suppressed in the endometriosis. Increased synthesis of estradiol and its availability further inhibits apoptosis by the activation of kinases which show enhanced sensitivity to estradiol in endometriosis. Resistance to progesterone is seen which further prolongs the survival of endometrial cells. A study was conducted in the patients of SLE to see if the severity of disease is less after menopause. Disease severity was markedly low after the menopause [59]. These studies suggest that estrogen (oral contraceptives, induction of ovulation etc.) should be very cautiously given to patients in auto immune diseases. It also suggests

future novel treatments should be targeted against immune modulation and focused on anti- estrogen and androgenic therapies.

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CONFLICT OF INTEREST

Authors declares no conflict of interest

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