

Study the Role of Hormones and Enzymes Aspect in Sera of Iraqi Endometriotic Patients Before and After Treatment with Diphereline

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Abstract

Endometriosis is a gynecological complication characterized by extra – uterine location of endometrial tissue , mainly in abdominal organs (including ovaries , bladder , intestine , kidney and in rare cases liver . Symptoms due to endometriosis may vary during the woman’s menstrual cycle as hormone levels fluctuate, in this regard , hormones play a central role in the aetiology of endometriosis since it is a disease of women in reproductive age and not usually seen in postmenopausal women. In women with endometriosis , the misplaced endometrial cells in the pelvic cavity also respond to these hormones. With the exception of the symptomatic treatment of endometriosis associated pain , only two main suboptimal therapeutic approaches (hormonal and invasive surgery). Diphereline is a single half dose depot Gonadotropin releasing hormone agonist (GnRHa) , which is long acting , GnRHa are a group of drugs that have been used to treat women with endometriosis for over 20 years , they are modified versions of naturally occurring hormones known as gonadotropin releasing hormones which helps to control menstrual cycle. This study have indicated the role of hormonal imbalance via the abnormalities in LH , FSH and PRO levels compared with healthy control , also our study have revealed that liver was not affected by endometrial lesions for enrolled patients via normal levels as AST and ALT. Lastly , the non significant difference in creatinine and urea levels compared with healthy control reflect that the kidneys were not affected by endometrial tissue. On the other hand , this study highlights Diphereline role in enhancing hormonal system in endometriotic patients (after treatment) , while has a negative side effect on liver and kidney via increasing of (AST and ALT) activities related to liver and (creatinine and urea) levels related to kidneys in sera of patients compared with control.

Keywords endometriosis: LH , FSH , PRO , AST , ALT , Diphereline.

1.0 Introduction

Endometriosis is a recurrent and benign gynecological disease (1) , include the abnormal growth of endometrial tissue outside the uterine cavity (2,3). Endometrial tissue is implanted in the abdominal cavity via transporting through lymphatic or blood vessels to organs including this at distance sites from the uterus (3,4) , mainly in pelvic organs (5). Some women may have a few endometriotic implants on the surface of the pelvic , the peritoneum , or pelvic organs , or they may invade the peritoneum and grow as nodules (6). Endometriosis tissue is biologically the same as basal endometrial tissue (2). The two primary clinical features of endometriosis are pelvic pain , dysmenorrhea and infertility , however , the relationship between endometriosis and infertility is strong (1,2). Despite differences in population characteristics, the definitive diagnosis of endometriosis requires laparoscopy along with surgeon expertise and interest , making it difficult to determine the exact prevalence. Because several medical societies do not recommended laparoscopy during an infertility workup , the epidemiology of endometriosis is further complicated (2). Broadly , gonadotropin releasing hormones (GnRHs) are produced by the hypothalamus of the brain , endogenous GnRHs , which in turn eliminates production of the pituitary gland hormones , follicle stimulating hormones (FSH) and luteinizing hormones (LH). In the absence of (LH) and (FSH) the gonads atrophy in both males and females (7). Evidence of pituitary – ovarian dysfunction has been found in endometriotic patients (1). Ovulatory dysfunction , luteinized unruptured follicle , abnormal luteal phase , increasing LH and FSH concentrations , as well , increased prolactin levels seen to be frequent among infertile women with endometriosis (3). Some investigators have suggested that relative hyperprolactinemia may be responsible for the infertility associated with endometriosis (8). Aspartate aminotransferase (AST) and Alanine Aminotransferase (ALT) are the most important liver enzymes that cause catabolism of amino acids , thus increase of these enzymes is attributed to liver , this increase of this enzyme indicates liver damage or too much pressure on liver , consequently these enzymes are used widely to show the

liver status in various diseases (9). Moreover ; kidney may be one of the affected organs in endometriotic patients (10). Serum urea and creatinine are markers of renal function. However , urea , creatinine and uric acid are neither very sensitive nor very specific markers of renal function , thereby become useful tools in the monitoring of the renal status of these (11). Body waste products like urea , creatinine and free water are removed from the blood , by kidneys in normal cases (12).With the exception of the symptomatic treatment of endometriosis associated pain , only two main suboptimal therapeutic approach as hormonal and invasive surgery are generally recommended to patients (5). Diphereline is a medicine belongs to gonadotropin releasing hormone analogues (GnRHa) medicines (13), these drugs are non steroidal compounds used widely in the treatment of endometriosis (14). Anyway , GnRH therapy causes long term pituitary down regulation after surgery in endometriotic patients. Although it has been advocated to improve the pregnancy rate , but its real value is still uncertain (15). Despite the large number of researchers related to endometriosis , its pathogenesis is still unknowledged , there is a lack of early diagnostic markers and current therapies are only symptomatic (1). The issue of the proper characterization of endometriosis as a disease , a clinical entity or pathology is still a topic of discussion today (16).

2.0 Materials and Methods (experimental)

2.1 Subjects

Forty (40) women suffering from endometriosis with the age (25-40) were enrolled in this study , who attended departments of Gynecology and obstetrics related to Baghdad teaching hospital / Medical city and Kamal Al-Samarray hospital from April to October 2013. Patients were divided into two groups , Group 1 (B) involved (20) newly diagnosed endometriotic patients (without any treatment) , diagnosed by laparoscopy and their reports revealed that liver and kidneys were not affected by endometriotic lesions. Second group (A) included (20) endometriotic patients who treated with diphereline (11.25 mg) for 6 months (one intramuscular injection of diphereline repeated every 3 months). Patients groups were compared with a healthy control group (C) , with the same range of age as patient groups , this group involved (20) healthy women.

2.2 Blood sampling and Parameters Determination

Five milliliters (5 mL) of venous blood were collected from all subjects enrolled in this study , placed into plain tubes until coagulation was performed , the later step is separation of serum from blood cells by centrifugation at 4000 r.p.m . The obtained sera was kept frozen until analysis . Determination of serum (LH) , (FSH) and (PRO) was performed by Enzyme linked Immunosorbent Assay (ELISA) for direct antigen detection using high affinity of Biotin for streotavidin which has been coated on the surface of microliter wells , the absorbance was measured at 450 nm. On the other hand , AST , ALT . urea and creatinine were determined via enzymatic methods.

2.3 Statistical analysis

The results were expressed as mean \pm SEM . Student t-test was applied to compare the significance of the difference between studied groups. ($p < 0.05$) , ($p < 0.001$) and ($p > 0.05$) considered statistically significant , highly significant and non- significant respectively.

3.0 Results

Table (1) shows the sera levels of LH , FSH and PRO in sera of studied groups. Our results have revealed that LH levels were highly significant increase ($p < 0.001$) in B (21.23 ± 0.12) mLU/mL compared with C (11.7 ± 0.21) mLU/mL , conversely , high significant decrease ($p < 0.001$) was observed in A (15.36 ± 0.21) mL U /mL compared with B (21.23 ± 0.21) mL U / mL. Also , a significant increase ($p < 0.05$) was seen in A(15.36 ± 0.21)

mL U /mL compared with C (11.7 ± 0.21) mLU/mL . The results also implied that FSH levels were highly significant increase ($p < 0.001$) in B (29.98 ± 0.16) mL U / mL and A (15.87 ± 0.22) mL U / mL compared with C (9.85 ± 0.24) mL U / mL , while highly significant decrease ($p < 0.001$) was noticed in A (15.87 ± 0.22) mL U / mL compared with B (29.98 ± 0.16) mL U / mL. Prolactin (PRO) levels were highly significant increase ($p < 0.001$) in B (26.79 ± 0.23) ng/mL compared with C (13.85 ± 0.78) ng/ mL , while non significant variation ($p > 0.05$) was noted in A (20.35 ± 1.24) ng/mL compared with B (26.79 ± 0.23) ng / mL and C (13.85 ± 0.78) ng/mL Results related to table (2) have implied that non significant difference ($p > 0.05$) was observed in AST activity (U/L) in sera of B (25.41 ± 0.16) U/L compared with C (26.3 ± 0.27) U/L , while high significant increase ($p < 0.001$) was found in A (39.35 ± 0.37) U/L compared with B (25.41 ± 0.16) U/L and C (26.3 ± 0.27) U/L. Also , ALT activity was non significant changed ($p > 0.05$) in sera of B (19.6 ± 0.18) U/L compared with C (18.13 ± 0.12) U/L , while a significant increase ($p < 0.05$) was seen in A (27.80 ± 0.55) U/L compared with B (19.6 ± 0.18) U/L. There were highly significant increase ($p < 0.001$) in A (27.80 ± 0.55) U/L compared with C (18.13 ± 0.12) U/L. Lastly , table (3) represent data related to urea and creatinine levels in sera of endometriotic patients and control groups , in this regard , there was non significant increase ($p > 0.05$) in urea level in sera of B (28.04 ± 6.87) mg/dL compared with C (26.05 ± 2.9) mg/ dL and A (24.68 ± 2.9) mg/dL , also non significant difference ($p > 0.05$) was noted in B (28.04 ± 6.87) mg/dL compared with A (24.68 ± 2.9) mg/dL. These results have also revealed non significant variation ($p > 0.05$) in creatinine level in B (0.577 ± 0.18) mg / dL compared with C (0.578 ± 0.23) mg / dL and A (0.697 ± 0.20) , and also in A (0.697 ± 0.20) mg/dL compared with C (0.578 ± 0.23) mg/dL .

Table 1. Levels of LH , FSH and PRO in sera of the studied groups

Parameter	C Mean \pm SEM	B Mean \pm SEM	A Mean \pm SEM	P B/C	P A/B	P A/C
LH (mLU/mL)	11.7 ± 0.21	21.23 ± 0.12	15.36 ± 0.21	H.S	H.S	S
FSH (mLU/mL)	9.85 ± 0.24	29.98 ± 0.16	15.87 ± 0.22	H.S	H.S	H.S
Prolactin (ng/mL)	13.85 ± 0.78	26.79 ± 0.23	20.35 ± 1.24	H.S	N.S	N.S

Table 2. Activities of AST and ALT in sera of the studied groups.

Parameter	C Mean \pm SEM	B Mean \pm SEM	A Mean \pm SEM	P B/C	P A/B	P A/C
AST (U/L)	26.3 ± 0.27	25.41 ± 0.16	39.35 ± 0.37	N.S	H.S	H.S
ALT (U/L)	18.13 ± 0.12	19.6 ± 0.18	27.80 ± 0.55	N.S	S	H.S

Table 3. Levels of urea and creatinine in sera of the studied groups.

Parameter	C Mean ±SEM	B Mean ±SEM	A Mean ±SEM	P B/C	P A/B	P A/C
Urea (mg/dL)	26.05±3.17	28.04±6.87	24.68±2.9	N.S	N.S	N.S
Creatinine (mg/dL)	0.578±0.23	0.577±0.18	0.697±0.20	N.S	N.S	N.S

4.0 Discussion

Endometriosis is one of the most frequent benign chronic gynecological disorders, and it influences female health negatively by causing abdominal pelvic pain and infertility (15). However, a previous study has reported that endometriosis is a heterogeneous disease, strongly associated with hormonal alterations (8). Anyway, abnormalities in gonadotropin dynamics in the later follicular phase or midcycle have been reported, but studies reporting on baseline gonadotropin levels in early follicular phase are scarce. Abnormal long or biphasic LH surges were reported; regarding FSH increased concentrations were reported (2). These findings are in agreement with our results related to high significant increase in LH and FSH levels in sera of endometriotic patients (without treatment / group B) compared with healthy control / group C, table (1). Broadly, LH supports theca cells in the ovaries that provide androgens and hormonal precursors for estradiol production, at the time of menstruation, FSH initiates follicular growth, specially affecting granulosa cells. With the rise in estrogens, LH receptors are also expressed on the maturing follicle which causes it produce more estradiol, in this regard, high levels of FSH are consistent with women who have ovarian failure (17), at this point, one of the important features in endometriotic patients is ovarian cyst (18). Also, a recent study has suggested that endometriosis may grow on the surface of the ovary as implants or invade the ovary and develop a blood-filled cyst called endometrioma or chocolate cyst (6). In this regard, a previous study has reported that endometriosis encountered in multiple sites including the ovaries (4). Further, a second study has also demonstrated that abnormal LH have been linked with endometriosis associated fertility, subfertile women with endometriosis have been reported to demonstrate impaired follicular growth, ovulatory dysfunction and distributed LH patterns (19). All the above explanations give a good support to our results related to high levels of LH and FSH in endometriotic patients compared with healthy control. Prolactin (PRL), a polypeptide hormone primarily known for its role in regulation lactation in humans and other mammals, is produced by the anterior pituitary and released into the blood stream. Extra pituitary PRL production has also been erected in a variety of tissues including the endometrium (20). Among the hormonal alterations associated with the endometriosis, hyperprolactinemia is one of the conditions most frequently mentioned in the literature. Many researchers have investigated the relation between serum prolactin levels and infertility in patients with endometriosis, but the results are controversial. At this point, it has been observed not only that ectopic implants of endometriosis secrete prolactin in a significant way, but also there is a significant positive association between prolactin secretion by ectopic endometrial cells and the scoring of endometriosis (8). Additionally, it has been reported that hyperprolactinemia (increasing of PRL upper than its normal value) is associated with ovulatory disturbances (17). The above studies gives a strong support to the high significant increase in prolactin levels in endometriotic patients (B) compared with healthy control (C).

Diphereline (triptorelin pamoate) is a gonadotropin releasing hormone (GnRH) agonist, the administration of diphereline results in hypogonadotropic amenorrhea (21). Gonadotropin releasing hormone (GnRH), is a small decapeptides that serves as an important connection between the neural and endocrine systems (22). Broadly, the gonadotropin-releasing hormone (GnRH) peptide used in GnRH in immunocontraceptives is secreted (in pulsative fashion) by the hypothalamus of the brain and stimulates the secretion of luteinizing and follicle-

stimulating hormones by the anterior pituitary gland, these hormones, in turn, activate hormone and gamete production by the ovary and by the testis. On the other hand, GnRH based immunocontraceptives (in non-pulsative fashion) cause the production of GnRH antibodies, thus preventing the production of sex hormones and ultimately inhibiting ovulation (23). For these reasons, LH and FSH were highly significantly decreased in group A compared with group B, table (1). Anyway, PRL levels were also decreased after treatment but this decrease was non significant. Results of table (1) have also revealed that diphereline acts a reactive role in modulating hormonal system, but this modulation not reached the normal value.

Aspartate amino transferase (AST) E.C (2.6.1.1) is a widely distributed enzyme, which is found in many tissues and organs, with high activity in the liver, increased AST activity in the serum is a sensitive marker of liver damage. Alanine amino transferase (ALT EC 2.6.1.2) is a sensitive marker of liver damage, and its increase in the blood plasma is specific for changes in the liver (24). As a result, livers of endometriosis patients enrolled in this study are not affected by endometriotic lesions. Although spread of these lesions through the abdominal cavity, non significant difference in group B compared with group A suggest that patients enrolled in this study have approximately a normal hepatic function. The absence of any hepatic abnormalities before treatment indicate that liver is not affected by endometriotic lesions and this is a good support for diagnosis by laparoscopy. However, a previous study has reported that although endometriosis is usually confined to the pelvis and reproductive organs but has been described in several remote sites including the omentum, gastrointestinal tract, peritoneum, operative scars, lymph nodes, umbilicus, skin, lungs, pleura, bladder, and pancreas. Anyway, hepatic endometriosis is extremely rare (25). The impact of GnRH analog therapy on liver function and metabolism is largely unknown, however, the present study have revealed a negative impact of diphereline on hepatic function because AST and ALT activities were highly significant and significant respectively increased in sera of group A compared with group B, table (2). Further, the high significant increase in group A compared with group C indicate that diphereline has a side effect on liver function. In this regard, a previous study has revealed that GnRHs significantly increase mean ALT and AST level from baseline (14). However, it has been investigated long term toxicity of the GnRH and noted a significant dose-dependent increase in AST and ALT activities, anyway, in some clinical reports, there are only a few cases of liver toxicity manifested by transiently elevated enzymes in a hepatocellular pattern AST and ALT (26). Anyway, the applied dose of analogs affected the morphology of the ovaries and uterus changed histological appearance of the liver and altered some metabolic processes in the pituitary gland and the liver (26).

Lastly, results of table (3) have revealed that urea and creatinine levels were non significantly different in sera of endometriotic patients (before treatment / group B) compared with (healthy control / group C). Anyway, serum creatinine is widely used in determination of renal failure, also urea undergoes renal tubular reabsorption by specific transporters. Although creatinine undergoes secretion into renal tubular fluid, this is very modest in degree (27). Broadly, urea and creatinine molecules help with the excretion of excess nitrogen. Urea which is synthesized by the liver, is a good marker of acute renal disease. Creatinine is useful as a longer-term marker of renal function; it mainly a rise from muscle so levels may be elevated after consumption of meat (28). As a result, kidneys of patients enrolled in this study were not affected by endometriosis, this suggestion gives a good support to the diagnosis by laparoscopy. However, endometriosis of kidneys is a rare manifestation of a relatively common disease (29). Results of table (3) have revealed a non significant difference in levels of creatinine and urea in sera of group A compared with group B, also non significant variation was noted between groups A and C, suggesting that kidneys related to enrolled patients were not affected not only by endometriotic lesions but also by treatment with diphereline which is a GnRH.

5.0 Conclusions

This study has indicated that LH, FSH and PRO are good biochemical markers in endometriosis. Further, this study has reported the positive and negative effects of diphereline in the treatment of endometriosis, however rare studies dealt with diphereline in the field endometriosis. The present study is a novel study in Iraq linked

between endometriosis and diphereline. It highlights diphereline role as a successful treatment for endometriosis via alternating hormonal balance. Nevertheless, it has a negative impact on AST and ALT. Lastly, the measured biochemical parameters via laboratory tests in this study give a crucial indication to the diagnosis by laparoscopy because activities of AST and ALT and levels of creatinine and urea in serum give a manifest evidence to the progression of endometriosis in the abdominal cavity.

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Biography

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