Prevalence of Endocrine Disorders among Iraqi Women with Menstrual Disturbances

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Abstract

Background and Objectives: The main causes of menstrual cycle disturbances are classified as hormonal abnormalities, structural abnormalities, bleeding diatheses, anovulation, polycystic ovary (PCO), obesity and miscellaneous. In this work, the prevalence of endocrine disorders in Iraqi women with menstrual disturbances was estimated.
Patients and Methods: One hundred Eighteen females with menstrual disturbances (delay>10 days occasionally) were included in this study in addition to thirty seven control women. They were attending to the gynecological clinics for regulation of menstruation cycle. The study excluded any women taking steroid hormones, neuroleptics, anticoagulants and cytotoxic agents that frequently lead to menstrual disturbances. Luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), prolactine, total testosterone, estradiol (E2) and progesterone were estimated in the second day of the menstrual cycle using ELISA technique using a ready for use kits.
Results: The endocrine disorders in menstrual disturbances in the Iraqi women under study were: 16.1% hypothyroidism, 3.4% hyperthyroidism, 3.4% type 1 diabetes mellitus, and pituitary tumor was observed in 1.6 % of patients. Additionally, there is a high prevalence of patients with POCS cases and a high significant increase in the mean of BMI in the patients when compared with the control women.
Conclusion: Surprisingly, the most common endocrine disorder in the women with menstrual disturbances group was hypothyroidism. Additionally the PCO is common in these women. The prevalence of endocrine disorders in irregular women in Iraq was lower than the other countries and the type of prevalent endocrine disorders is different.

الخلاصة

المقدمة وهدف الدراسة: تصنف الأسباب الرئيسية لاضطرابات الطمث إلى اضطرابات هرمونية وتشريحية واضطرابات النزف والاباضة ومتلازمة تكيس المبيض والسمنة وأسباب أخرى. في هذه الدراسة تم تقدير شيوع الأسباب الهرمونية عند مريضات اضطراب الطمث في العراق.
المرضى وطرق العمل: اشترك في هذه الدراسة 108 أنثى لديهن اضطراب الطمث (تأخير في نزول الدم أكثر من 10 أيام) بالإضافة إلى 37 أنثى سليمة كمجموعة سيطرة. هؤلاء المرضى كانوا يراجعن عيادات الأمراض النسائية لتنظيم الدورة الشهرية لديهن. استثنت الدراسة أي مريضة تتناول علاجات ستيرويدية أو عصبية أو مضادات التخثر أو الأدوية ذات السمية الخلوية. أجريت القياسات الآتية على المريضات في ثاني أيام الدورة الشهرية (هرمون LH و الهرمون المحفز للجر يبات FSH و الهرمون المحفز للدرقية TSH و البرولاكتين و التستوستيرون الكلي و الاسترادايول و البروجستيرون) باستعمال تقنية الايلايزا.
النتائج: توزعت الأسباب الهرمونية اضطرابات الطمث كالآتي: قصور الدرقية 16.1% , فرط الدرقية 3.4% , السكر من النوع الأول 3.4%, أورام الغدة النخامية 1.6%, بالإضافة إلى انتشار تكيس المبيض وزيادة معامل كتلة الجسم BMI عند مجموعة المرضى مقارنة بمجموعة السيطرة.

الاستنتاج: كانت النسبة العالية من مريضات اضطراب الطمث لديهن قصور الغدة الدرقية وهذه نتيجة غير متوقعة كونها لم تسجل سابقا. كما ان تكيس المبيض شائع لدى المريضات. كما خلصت الدراسة الى ان نسبة انتشار الاسباب الهرمونية لاضطرابات الطمث كانت اقل لدى العراقيات مقارنة بدول اخرى ومختلفة عن النماط الموجودة في العراق.

Introduction

The menstrual cycle is a repetitive expression of the interaction of the hypothalamic-pituitary-ovarian system with associated structural and functional changes in the target tissues: uterus, oviducts, endometrium, and vagina of the reproductive tract. These processes require a balance of hormonal stimulation and withdrawal that associated endometrial growth and shedding. It is generally agreed that the normal menstrual cycle is between 24 and 35 days although a slightly boarder range of 28±7days is traditionally taught. The length or duration of the average menstrual period is 3 to 7 days [1, 2].

Menstrual disturbance refers to abnormal changes in menses arising from gynecologic causes other than pregnancy. It is a group of disorders characterized by dysfunction of the uterus, ovary, pituitary, hypothalamus or other part of the reproductive system, which results in abnormal or excessive uterine bleeding [3].

The main causes of menstrual cycle disturbances are classified as hormonal abnormalities, structural abnormalities, bleeding diatheses, anovulation, polycystic ovary (PCO), and obesity and miscellaneous [4, 5]. Endocrine causes of menstrual disturbances are very important because the menstruation cycle is hormonally directed state and any change in the level of the related hormones may affects the cycle rhythm. For instance, women with type 1 diabetes are likely to report menstrual disorders, including a later age at menarche [6]. Additionally, both hyper- and hypothyroidism may result in menstrual disturbances. The most common manifestation is simple oligomenorrhea and anovulatory cycles, which are very common. Increased bleeding is rare in hyperthyroidism [7]. Hormonal abnormalities are mainly due to hyperprolactinemia or failure to release gonadotropin-releasing hormones [8, 9]. Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis and presenting most commonly with amenorrhea and galactorrhea [10]. The main causes of hyperprolactinemia are pituitary tumors (usually prolactinomas), primary hypothyroidism, hypothalamic diseases, and ingestion of drugs that block the prolactine-inhibitory effects of dopamine [11, 12]. Many cases of hyperprolactinemia are classified as idiopathic [13, 14, 15].

Luteinizing hormone (LH) and follicle stimulating hormone (FSH) function to regulate gonadal steroid hormone biosynthesis and initiate and maintain germ cell development. Gonadotropin release is under negative and positive feedback regulation by estradiol, progesterone, and inhibin A and B. Progesterone and estradiol act in both the hypothalamus and the pituitary axis. Inhibin act at the level of the pituitary by suppressing FSH but not LH [16, 17].

This study was performed in order to diagnose and estimate the prevalence of the endocrine disorders (if present) in Iraqi women with abnormal menstruation cycles. The finding of the present work may affects the way in which the physician thinking when they treat menstrual disturbances by taking in the mind the possibility of hormonal disorder as a possible target for treatment.

Materials and Methods

1. Subjects:-

One hundred Eighteen females with menstrual disturbances (delay>10 days occasionally) were included in this study. Age range was (18-43) years. They were attending to the gynecological clinics for

regulation of menstruation cycle. All women were informed about the work under the supervision of their gynecologist and the results obtained (especially endocrine disorders) were provided to their gynecologist as an extra toolfor diagnosis and treatment.

The patients were evaluating using pelvic ultrasonography, to detect the presence of polycystic ovary (PCO) or pregnancy, and magnetic resonance imaging (MRI) to detect any pituitary tumors.

The study excluded any women taking steroid hormone, neuroleptics, anticoagulants and cytotoxic agents that frequently lead to menstrual disturbances [2, 3].

Thirty seven normal females with normal regular menstrual cycle and normal body mass index were included in the study as a control, their ages ranged from 16-39 years. They were not complaining of any other endocrine disorders and they have no history of systemic diseases.

BMI of both groups were measured using a mathematical formula (BMI=Kg/m2) [18], where weight in kilograms divided by height in square meters.

2. Blood Sampling:-

Ten milliliters of venous blood were collected from both groups of patients, centrifuged after clotting at 3000 rpm for 5 minutes. The serum then separated and stored in three aliquots in disposable tubes and frozen until assay.

3. Hormonal Assay:-

Luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), prolactine, total testosterone, estradiol (E2) and progesterone were estimated in the second day of the menstrual cycle using ELISA technique using a ready for use kits supplied by Biocheck® Company (USA). The procedure for estimation of each hormone was obeyed precisely as described in the leaflet supplied with the kit.

4. Statistical Analysis:-

Descriptive statistics (mean ± standard deviation (SD)) were used to evaluate the characteristics of the patients. Pooled Student's t-test was used to compare the results of the subjects. When (p-value<0.05), the relation considered to be significant.

Results and Discussion

The results showed that the majority of patients were in the reproductive age (data not cited). The age range (18-39years) with a mean of (23years). Moreover, it was clear that menstrual disturbance patients between (40-43) years were about 4% (n=5). The above results agreed with the observation of other studies [19, 20, 21] which found that menstrual disturbances were more common in the reproductive age or adult age groups range (20-39) years. Pelvic ultrasound examination showed that 35% of the irregular women were having PCO.

Figure (1) showed that, 16.1% of patients having hypothyroidism, 3.4% having hyperthyroidism, 3.4% having type 1 diabetes mellitus, and pituitary tumor was observed in 1.6 % of patients. These results were lower than those observed by Krassas *et al* (1999) [19] who found that 23.4% of hypothyroid patients had menstrual disturbance due to decreased metabolic clearance rate of androstenedione and estrone and an increase in peripheral aromatization. The percentage of hyperthyroidism was also lower than the percentage observed by others [20] who found that 21.5% of hyperthyroid patients had menstrual disturbance because metabolic clearance rate of estradiol was decreased in hyperthyroidism due to increased binding of estradiol to SHBG, mean plasma levels of testosterone and androstenedione were elevated. The production rate of testosterone and androstenedione were significantly elevated, and the conversion ratio of androstenedione to estrone, and

testosterone to estradiol, were increased [20].

Another study found that 21.6% of diabetes mellitus type 1 patient had menstrual disturbance, it had been suggested that GnRH pulse generator in the hypothalamus was responsible for diabetic menstrual dysfunction [21].

The research also noticed that there is a highly significant increase in BMI (P<0.01) in hyperprolactinema patients (33.6±5.8 kg/m^2) and normal prolactine women (30.1±6.7kg/m^2) in comparing with the control (22.4±3.6 kg/m^2). The above results showed the effect of increased BMI which referred to the high prevalence of obesity in the hyperprolactinemia patients [22] but the nature of this link stills poorly defined. While others explained the weight gain as a part of a neuroendocrine response to the environmental stimuli characterized by hyperprolactinemia [23].

The data illustrated by Table (1) clearly showed a highly significant decrease (P<0.01) in the concentration of estradiol in patients with normal prolactine and hyperprolactinemia (57.1±49.6 and 88.6±28.7 pg/ml) respectively, in comparing with normal control (88.6±28.71pg/ml). While no significant difference noticed (P>0.05) in the concentration of estradiol in both normal prolactine and hyperprolactinemia patients.

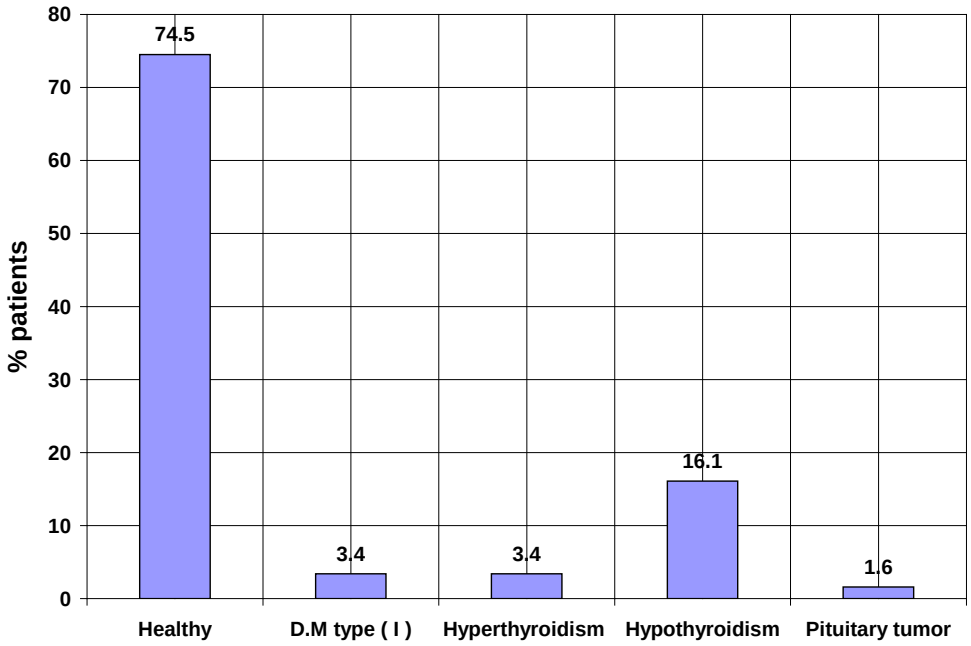

Figure 1. The percentages of endocrine disorders in women with menstrual disturbances.

Table 1. Mean±standard deviation of the hormones involved in ovarian functions: Estradiol, Progesterone & Total Testosterone in the studied groups.

Studied groups		Estradiol pg/ml	Progesterone ng/ml	T.Testosterone ng/ml
Normal Control		88.6±28.7	14.96±11.4	0.39±0.2
Patients	Normal prolactin	57.1±49.6 (P<0.01)	6.9±8.5 (P<0.01)	1.2±1.6 (P<0.05)
	Hyperprolacinemia	45.5±33.8 (P<0.01)	6.9±7.8 (P<0.01)	1.5±1.7 (P<0.01)
Normal vs. Hyperprolacinemia		(P>0.05)	(P>0.05)	(P>0.05)

elevated prolactine, since high level of prolactine completely blocks binding of FSH to its receptor on granulosa cell leading to the suppression of progesterone production [26].

The distribution of patients with PCO and non-PCO women according to the mean concentration of anterior pituitary gland hormones were listed in Table (2). It was noticed that the mean concentration of TSH in patients with PCO and non-PCO women (3.74±7.4 and 8.0±18.09µIU/ml) respectively, revealed no significant difference (P>0.05) when in comparing with normal control level (3.27±1.25 µIU/ml). Furthermore, there is no significant difference (P>0.05) in the mean concentration of TSH between in PCO and non-PCO women. The above results of TSH were screening tests for thyroid function [27] only and have no correlation between PCO and TSH.

Serum prolactineee level was significantly higher (P<0.01) in patients with PCO and non-PCO women (24.11±22.20 and 19.18±17.84 ng/ml) when compared with normal control (10.62±2.023 ng/ml). While a comparison between PCO and non-PCO women groups showed no significant difference (P>0.05) between them.

The concentration of estradiol was highly lowered in hyperprolactinemia patients compared with the control groups. These findings are in a good agreement with other studies [24] that found that high prolactine concentration had profound effect on steroidogenesis and inhibit secretion of estrogen by blocking the action of LH on the ovary. While decreased concentration of estradiol in other patients with normal prolactine associated with increased pituitary gonadotropin concentration (hypergonadotrophic hypogonadism) was observed in patients with ovarian failure which is responsible for this in some patients [25].

A highly significant decline (P<0.01) in progesterone concentration was observed in the normal prolactineee and hyperprolactinemia patients (6.95±8.5 and 6.86±7.7 ng/ml) respectively when compared with normal control (14.96±11.4ng/ml). Additionally there was no significant difference (P>0.05) between progesterone concentration in normal prolactine and hyperprolactinemia patients.

Hyperprolactinemia-associated luteal phase dysfunction may reflect the suppressive effect of inappropriately

Table 2. Mean±standard deviation of the hormones TSH, prolactine, LH, & FSH in the studied groups according to U/S (PCO) .

Studied groups	TSH µIU/ml	Prolactin ng/ml	LH mIU/ml	FSH mIU/ml
Normal Control	3.27±1.25	10.62±2.023	5.38±1.72	3.4±1.0926
Non-PCO	8.0±18.09 (P>0.05)*	19.18±17.84 (P<0.01)*	27.81±42.56 (P<0.01)*	19.7±34.11 (P<0.01)*
PCO	3.74±7.4 (P>0.05)*	24.11±22.2 (P<0.01)*	30.89±40.85 (P<0.01)*	13.22±14.19 (P>0.05)*
Comparison PCO *vs.* Non PCO	(P>0.05)	(P>0.05)	(P>0.05)	(P>0.05)

(*): Compared with control group.

elevations of both prolactine and thyrotropin levels. These results supported the hypothesis of pathogenesis of PCO, which is due to a central deficiency in dopaminergic activity at the basal hypothalamus [28]. However, increased prolactine concentration in non-PCO patients related to patients with

Table (3) showed the mean distribution of TSH, prolactineee, LH and FSH hormones in the studied groups. These results agreed with a study done by Luciano *et al* [28] who observed that hyperprolactinemia in PCO patients is due to a greater deficiency of hypothalamic dopamine as manifested by the basal

ovarian failure [29] and some patients have PCO as mentioned later. A mean concentration of total testosterone showed a highly significant increase (P<0.01) when we compared between hyperprolactinemia and normal control (1.49±1.72 and 0.39±0.197ng/ml) respectively. Also a significant increase (P<0.05) was noticed in comparison of total testosterone concentration between normal prolactine patients (1.17±1.6ng/ml) and normal control (0.39±0.197ng/ml). While no significant difference (P>0.05) noticed between testosterone concentration in normal prolactine and hyperprolactinemia patients.

hyperprolactinemia as mentioned previously in Table (3).

The data demonstrated in Table (4) clearly showed a highly significant decrease (P<0.01) between the mean concentration of estradiol in patients with and without PCO (55.37±38.18 and 52.61±49.47 pg/ml) respectively, in comparing with normal control (88.6±28.71 pg/ml). While no significant difference (P>0.05) found between the mean concentration of estradiol in patients with and without PCO. Decreased concentration of estradiol and progesterone in normal prolactine patients with elevated gonadotropins shown in Table (4) reveals that these patients have

Table 3. Mean distribution of (TSH, prolactine, LH & FSH) hormones in the studied groups .

Studied groups		TSH µIU/ml	Prolactin ng/ml	LH mIU/ml	FSH mIU/ml
Normal Control		3.27±1.253	10.62±2.023	5.38±1.724	3.40±1.092
Patients	Normal prolactin	5.49±13.6 (P>0.05)	11.13±4.99 (P>0.05)	29.56±35.9 (P<0.01)	19.88±30.37 (P<0.01)
	Hyper prolacinemia	8.89±18.82 (P>0.05)	44.05±21.17 (P<0.01)	27.34±53.8 (P<0.05)	11.7±24.38 (P>0.05)
Normal prolactin * Hyperprolacinemia		(P>0.05)	(P<0.01)	(P>0.05)	(P>0.05)

Table 4. Mean distribution of hormones involved in ovarian functions (Estradiol, Progesterone &Total Testosterone) according to U/S (PCO).

Studied groups	Estradiol pg/ml	Progesterone ng/ml	Total Testosterone ng/ml
Normal Control	88.6±28.71	14.96±11.4	0.39±0.197
Non-PCO	52.61±49.47 (P<0.01)*	6.48±7.21 (P<0.01)*	0.83±0.99 (P>0.05)*
PCO	55.37±38.18 (P<0.01)*	7.74±9.95 (P<0.01)*	2.09±2.22 (P<0.01)*
Comparison PCO *vs*. Non PCO	(P>0.05)	(P>0.05)	(P>0.05)

(*): Compared with control group.

Pelvic ultrasound examination showed that 35% of the irregular women were having PCO. The above results showed prevalence of PCO in both ovaries in Iraqi women with menstrual disturbance was higher than the prevalence of PCO in other studies in women with reproductive age [30, 31, 32].

The above results agreed with other study [33]. which observed that the imbalance of the gonadotropic hormones resulted in the pronounced degeneration of granulosa and theca cells, which leads to a decrease in the estradiol, and progesterone production and an increase of the androgens level [33].

Conclusion

High prevalence of patients with POCS cases at the age range (20-29& 30-39) years was observed. A highly significant increase in the mean of BMI in the patients when the results compared with the control. The prevalence of endocrine diseases in women with menstrual irregularities was: 16.1% hypothyroidism, 3.4% hyperthyroidism, 3.4% type 1 diabetes mellitus, and pituitary tumor was observed in 1.6 % of patients. Surprisingly, the most common endocrine disorder in the studied patients was hypothyroidism. Additionally PCO was common among these enrolled patients.

Elevation of LH and FSH concentration, with lowered estradiol and progesterone concentration give a picture of ovarian failure in patients with hyperprolactinemia or polycystic ovary syndrome. No significant differences (P>0.05) of FSH in patients with hyperprolactinemia and/or polycystic ovary syndrome when the results compared with normal control. Elevated LH and total testosterone concentration with lowered levels of estradiol and progesterone concentration in patients with PCO was also observed.

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