The Predictive Value of Serum Progesterone and Estrogen Recepters as Diagnostic Tool for Premature Ovarian Failure

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Abstract

Background: Premature ovarian insufficiency (POI) is a delicate medical problem in young women. This condition is not unchangeable and permanent but is associated with intermittent and unpredictable ovarian activity, resulting in low conception rate. Over the period of 8 years, the evaluation of secondary amenorrhea was conducted in 90 patients below the age of 40 who wished to restore fertility and is characterized by irregular or absent periods and reduced fertility. Symptoms include those associated with the natural menopause (night sweats and vaginal dryness), and with the long-term adverse effects of estrogen deficiency (osteoporosis and cardiovascular disease): The latter is believed to explain the shorter life expectancy associated with POI.

Aim: To illustrate the predictive value of progesterone receptors (PRs), estrogen receptors (ERs), progesterone (PRG), estradiol (E2), Lulilizing hormones (LH), Follicle stimulating hormones (FSH) and Anti mullerian hormones (AMH) serum levels as diagnostic approach for POI.

Method: Sixty (60) women with idiopathic POF with thirty (30) women as control groups were included in the study. Baseline investigation in all subjects included serum progesterone receptors(PRs), estrogen receptors(ERs), progesterone (PRG), estradiol (E2), Lulilizing hormones (LH), Follicle stimulating hormones (FSH) and Anti mullerian hormones (AMH) levels were estimated using appropriate assays in biochemistry laboratory.

Results: There was statistically significant differences in the serum progesterone receptors, estrogen receptors, progesterone, estradiol, LH, FSH and AMH in POI cases when compared with healthy control (P=<0.05).

Conclusion: These results indicate that serum progesterone and estrogen receptors levels, is high in POI cases as a result of lack progesterone and estradiol hormones as a result of loss negative feedback inhibition,this result may be used to primary diagnosis of premature ovarian failure.

Keywords: *Premature ovarian failure (POF), Anti mullarian hormones(AMH), progesterone receptors (PRs), Estrogen receptors (ERs).*

Introduction

Premature ovarian insufficiency (POI) is an early event in the reproductive life span with a significant impact on several dimensions of women's well-being and general health[(1)]. It affects 1% of women under age 40 years, 0.1% of women under age 30 years, and 0.01% of women under 20 years of age[(2)]. POI prevalence appears to vary by ethnicity, being higher in women from African and Latin American countries[(3)]. Such terminology describes the spectrum of conditions associated with the loss of ovarian function prior to the natural age of menopause. It includes both spontaneous POI and those situations in which POI derives from iatrogenic interventions such as radiation therapy, chemotherapy, or surgery. Women with POI may

display established premature menopause or present with intermittent residual ovarian function[4]. The premature hormonal deficiency may be of unknown origin or may be the result of several etiologies, including genetic, autoimmune, metabolic, and infective causes, which lead to ovarian follicular dysfunction or depletion of functional primordial follicles[5] . Spontaneous early menopause affects approximately another 5% of women between ages 40 and 45 years[6] . Moreover, even though the rate of bilateral oophorectomies routinely performed at the time of hysterectomy is declining, a significantly high number of women still enter menopause earlier due to bilateral oophorectomy performed for treatment of ovarian pathology or for prophylactic purpose in women genetically predisposed to breast and ovarian cancer[7] . The percentage of cancer survivors has also increased over time because of improved success in the treatment of cancer in children, adolescents, and reproductive-age women[8] . Therefore, early hormonal deprivation occurs in a large number of women and the short-term and long-term consequences are variable, depending mainly on age at onset and type of POI[9,10]. Importantly, these consequences may include the burden of infertility and the management of fertility preservation[11]. POI is usually diagnosed when two follicle stimulating hormone levels in the menopausal range (>30 U/l), at least 1 month apart in the setting of 4–6 months of amenorrhea, are documented[12]. A timely diagnosis and a tailored hormonal treatment at least until the average age at natural menopause occurring around 50 years are mandatory to relieve menopausal symptoms, and to prevent osteoporosis, cardiovascular risks, and neurocognitive disorders[13] and the increased risk of overall mortality in women with early experience of menopause[14]. On the other hand, POI requires adequate counseling at multiple levels, including psychosocial and sexual consequences, because there is an acceleration of the aging process. Indeed, hormonal replacement is not always entirely able to relieve the multitude of implications for women who have to move forward with their own lives in a POI state[15].

Cytosol estrogen and progesterone receptors are present in many organs including the breasts, endometrium, myometrium, cervix, fallopian tubes and ovaries. The ovaries are not only a source of estrogen and progesterone but they appear to be targets for these hormones[16,17]. Estrogen is considered a primary culprit in the development of ovarian cancer as 70% of ovarian cancers express estrogen receptors (ERs), whereas progesterone and itsreceptor are protective against ovarian cancer[18,19]. In patients with cancers of the breast and endometrium the relationship between tumor estrogen and progesterone receptor (PR) levels and prognosis is well documented. However, the clinical significance of ER and PR content in ovarian carcinomas has not been well established[16,20].Anti-Müllerian hormone (AMH), also known as Müllerian inhibiting substance (MIS) or factor (MIF), has well defined roles in male sex differentiation. Across the female reproductive lifespan the role of AMH has, however, only more recently come to light. AMH is produced by granulosa cells (GCs) in small, growing ovarian follicles, and plays an important role in folliculogenesis. AMH correlates to functional ovarian reserve, and is, therefore, used as a diagnostic and prognostic marker in infertility and in reproductive disorders like polycystic ovary syndrome (PCOS) [21], and primary ovarian insufficiency (POI) [22]. Understanding AMH actions may, therefore, provide insights into follicular development under normal as well as pathophysiological conditions.

Recent studies have indicated that follicular growth is regulated by subtle interactions between gonadotropins (FSH and LH) and local factors produced by the theca and granulosa cells [23]. FSH receptors are expressed in granulosa cells at the primary follicle stage, and they are required for follicular development into the pre-antral stage [24]. FSH activity also increased the primordial pool and enhanced the early follicle stock [25]. LH triggers granulosa wall dissociation and cumulus expansion as well as oocyte nuclear maturation [23].

Materials and Method

Study population and sample collection: The Women included in the present study were gathered from those attending Obstetrics and Gynecology Clinic in Kalar General Hospital, Kalar. The study conducted during the period from June 2019 to January 2020 and total of 60 POF women and 30 apparently healthy matched were included in the study. In this study, the eligibility criteria for POF cases included: (1) under 40 years of age at the first time of diagnosis; (2) amenorrhea for at least 4 months; (3) an increased FSH level >25 IU/L on two occasions >4 weeks apart; (4) patients with known causes of POF (such as karyotypic abnormalities, ovarian surgery, and autoimmune diseases etc.) were excluded. The eligibility criteria for the controls included: (1) healthy women with regular menstrual cycles; (2) without hormonal therapy in the last six months; (3)

without endocrine system diseases, such as polycystic ovary syndrome, thyroid, and hyperprolactinemia etc. Peripheral blood of patients was collected at the time of interview with a structured questionnaire. Venous blood of patient women was collected so that the control . The blood was centrifuged immediately at 3000 r/min for 10 min, and the serum was collected in a polypropylene tube. The samples were stored at 80 C for further chemical analysis and hormone measurement.

Biochemical analysis: The serum progesterone receptors (PRs), estrogen receptors (ERs), Lulilizing hormones (LH), Follicle stimulating hormones (FSH) and Anti mullerian hormones (AMH) progesterone(PRG), estradiol (E2), levels were measured by an automated Roche Modular Analytics E411 immunoassay system (Roche Diagnostics, Mannheim, Germany). Inter and intra-assay coefficient of variations (CVs) for all the tested hormones was less than 10%.

Statistical analysis: The obtained data were analyzed using IBM SPSS statistical package (version 20). Student's t test was applied to calculate significance of differences between patients and controls groups.

Results

Determination the serum progesterone and estrogen receptors: The results of the present study showed significant elevation (P<0.05) in the mean serum level of progesterone receptor in women with POI (4.14±0.42 ng/ml), when compared to control group (2.44±0.33 ng/ml). The serum level of estradiol receptor demonstrated significant elevation in POI cases (4969.92±271.51 pg/ml),when compared to control group (551.17±59.91 pg/ml), Table (1) .

Table (1): Serum progesterone and estrogen receptors in patient cases and controls

Parameter	Patient			Control			P
	Mean±Se	Max	Min	Mean±Se	Max	Min	
PRs ng/ml	4.14±0.42	13.27	0.11	2.44±0.33	8.32	0.15	0.001
ERs pg/ml	4969.92±271.51	8000	360	551.17±59.9	1198	50	0.003

Determination the serum LH, FSH and AMH: The LH and FSH mean serum levels were significantly (P<0.05) higher in women with POI,(43.36 ±3.01, 62.15±3.98 mIu/ml) as compared to controls (6.06±0.40, 6.00±0.31 mIu/ml,) respectively. However, AMH mean serum level (0.16±0.03 ng/ml) was significantly (P<0.05) lower in women with POI than that in controls (2.72 ±0.16), Table (2).

Table (2): Serum LH,FSH and AMH in patient cases and controls

Parameter	Patient			Control			P
	Mean±Se	Max	Min	Mean±Se	Max	Min	
LH mIu/ml	43.36 ±3.01	100.87	10.23	6.06±0.40	9.79	3.12	S
FSH mIu/ml	62.15±3.98	181.32	22.28	6.00±0.31	11.15	2.97	S
AMH ng\ml	0.16±0.03	0.91	0.01	2.72±0.16	4.55	1.29	S

Determination the serum progesterone and estradiol: Both Estradiol and progesterone mean serum values were significantly (P<0.05) lower in women with POI (8.75±0.75 pg/ml, 0.23±0.03 ng/ml) than in controls (56.06±4.11 pg/ml, 0.60±0.04 ng/ml) respectively, Table (3).

Table (3): Serum progesterone and estradiolin patient cases & cotrole

Parameter	Patient			Control			P
	Mean±Se	Max	Min	Mean±Se	Max	Min	
Estrogen pg\ml	8.75±0.75	19.99	0.32	56.06±4.11	102.11	22.36	0.002
Pregesterone ng\ml	0.23±0.03	0.95	0.01	0.60±0.04	0.99	0.24	0.003

Discussion

In the present study the mean serum level of progesterone (PR) and estradiol receptor (ER) was significantly higher in women with POI as compared to controls. This result was conflicting with the result of Kalpokas, Irene, et al[26]. The high levels of progesterone (PR) and estradiol receptors (ER) may be attributed to low serum levels of progesterone and estradiol which were as a result of ovarian dysfunction to produce this hormones. Additionally, the present study indicated a higher significant serum levels of FSH and LH in women with POI than in normal controls. Thus high serum levels of FSH and LH in clinical settings must take in consideration POI as the underlying aetiology. Reduced serum level of AMH in women added another tool for the diagnosis of POI. The result of present study was in agreement with the finding reported by YE, Xiaoqing, et al[27]. The high levels of LH and FSH may be as a result of loss the negative feedback inhibition that induced by progesterone and estradiol hormones.

The mean value of serum progesterone showed lower significant difference in POI cases when compared with healthy control. The present was in agreement with that reported by Czyzyk, Adam, et al[28] and Bemardi, F., et al.[29]. The low serum levels of progesterone and estradiol may be attributed to failure of the ovary to produce them.

Conclusions

Women with POI patient demonstrated significantly high mean serum levels of progesterone and estrogen receptors than healthy control, suggesting possibility of their use as biomarkers for the diagnosis of POI.

Conflict of Interest: Nil

Source of Funding: Self, from Kalar Health Authority.

Ethical Clearance: The study design approved by the Ethical Committee of Tikrit University College of Medicine and informed consent was taken from each participant before enrollment in the study

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