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MEDICAL GROUP

GLOBAL JOURNAL OF
Fertility and Research

ISSN: 2640-7884 DOI: https://dx.doi.org/10.17352/gjfr

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Received: 02 August, 2019
Accepted: 13 September, 2019
Published: 16 September, 2019

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Keywords: POF: Premature Ovarian Failure; Medical disorders

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Research Article

Prediction of Premature Ovarian Insufficiency and prevalence of medical diseases

Abstract

Background: Premature Ovarian Failure (POF) represents 1% among women below the age of 40 and can be diagnosed by two levels of serum Follicular Stimulating Hormone (FSH) ≥40mIU/mlat 6 weeks apart. There are many reasons for POF and commonly is idiopathic (60% to 80%). POF has a negative impact on the psychological, social and quality of life of females.

Objective: This study aims to find the possibility of prediction of Premature Ovarian Insufficiency (POI) and its relation to medical disorders.

Materials and methods: A retrospective study was conducted at the National Center for Diagnosis and Treatment of Infertility- Misurata, Libya. A total of 350 patients with POI were involved. The Inclusion Criteria were: age <40 years, with high serum FSH level, low Anti-Mullrian Hormone (AMH) and low Antra-Follicular Count (AFC). The hormonal essay including FSH, Luteinzing Hormone (LH), Estradiol (E2), Thyroid-Stimulating Hormone (TSH), Prolactin and Fasting Blood Sugar (FBS) along with the medical history was collected.

Results: Overall collected cases had a mean age (31.19±3.86 years) and the medical disorders represented 47% of POI causes. Hypothyroidism, Hyperprolactinemia and Diabetes Mellitus were the most common associated disorders (31%, 30%, 14% respectively). The increase in the level of FSH (14.78±12.87) was the most sensitive test to predict POI especially in hypothyroidism cases, which could help to predict ovarian failure in those groups of people.

Conclusion: There is a strong association between POI and medical conditions especially Hypothyroidism. Changes in FSH are the most sensitive test among ovarian markers to predict POF.

Introduction

POF can be considered as an end stage of multiple disorders that ends by loss of ovarian function [1]. However, there are other terms that include POI, when the condition is different because there may be intermittent and unpredictable resumption of the ovarian activity [2].

Insufficient ovarian reserve is usually associated with a disturbance in the FSH, AFC and AMH. However, the cycle is still maintained as normal [3]. Accordingly, there is the possibility of Transitional Ovarian Failure (TOF) which takes 3 to 10 years to develop into POF and is characterised by abnormalities in some ovarian reserve markers mainly FSH elevation >10.2IU/litre, AFC <5 follicles and AMH <0.5 to 1.1ng\ml with a regular cycle [4].

Some human organs are affected by medical disorders leading to disruption of their function and one of these is the ovary [5]. These health problems generally involve chromosomal, autoimmune, iatrogenic, environmental, metabolic (diabetes type 1, thyroid disease, etc.), endometriosis and hyperprolactinemia (Pituitary tumours, such as adenoma) [6]. In addition, the Autoimmune Polyglandular Syndromes (APS) is a collection of problems that involve mainly an adrenal insufficiency, thyroid disease, type 1 diabetes mellitus, and is probably associated with POF [7].

Studies have revealed the prevalence of endocrine abnormalities among POF patients and these are mostly referred to a thyroid problem being the most common cause of POF in its relation to other medical problems [8]. However, most of the prior studies have not been concerned with the possibility of the prediction of POF. On other hand, a few studies have indicated no statistically significant difference with regard to the most sensitive indicators for the prediction of POF as

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most of the cases were diagnosed as end stage ovarian failure [9,10].

It is a fact that the diagnosis of POF is usually late because there will be an exhausted follicular supply for a period of time [11]. Consequently, POF will have a negative impact on the psychological, social and the quality of life among females. However, the prediction of POI in some situations is still under research as it is necessary to fully understand the aetiology and pathogenesis of POI [6]. Such understanding could provide early management of cases that could provide the possibility of preserving ovarian function for a period of time [12,13]. This study aims to detect the association of POI with medical diseases and its possibility of prediction in certain cases.

Materials and Methods

A retrospective study was conducted at Misurata National Center for Diagnosis and Treatment of Infertility- Misurata, Qaser Ahmed, Residential City, Misurata, Libyawhereby 350 patients with POF were included in the study. The Inclusion Criteria included: age <40 years, with high serum (FSH>12mIU/ml) level, low (AMH<1ng/ml) and low (<5AFC). The data included in the study were age, primary or secondary infertility, TSH, FBS, Prolactin, any pelvic surgery, family history of POF and history of any medical illness.

In this study, the AMH measurement was undertaken by the immunoassay supplied by Diagnostics Systems Laboratories (DSL) (a Roche Hitachi) that has a sensitivity of 0.043pmol/l (0.006ng/ml). FSH was measured by Electro Cheiluminescence Immuno using (Beckman Coulter Inc). The AFC and normal anatomy of pelvic organs were determined by performing trans-vaginal ultra-sonography (TVS).

Statistical analysis

The data was analysed by software SPSS 23.0. Descriptive statistics were presented in terms of minimum, maximum, mean ± standard deviation for continuous variables, whereas the categorical data was presented by counts (percentage). The significance of correlation between variables was calculated by the student's t-test and Fisher test. The statistical significance was taken as p-value ≤0.05.

Results

In the present study, the total number of patients with POF was 350. The mean age of cases was 31.19±3.86 years and 67% of cases had primary infertility while 23% had secondary infertility. One of the important signs of POI is cycle irregularity and in the present study this was seen in 102 patients (29.1%). Only four patients with POF had a positive family history. All this general data is given in Table 1.

The medical disorders represented 167(47%) and were mostly Hypothyroidism (31.1%), hyperprolactinemia (29.9%) and Diabetes Mellitus (13.9%). There were 12(7.2%) cases with both Hypothyroidism and Hyperprolactinemia. There was only one case with celiac disease, one with vitilligo, one has Systemic Lupus Erythematosis and one has chronic hepatitis B virus. Three cases were documented with skin disease on steroid therapy. Table 2 represents this information.

The other cases of POF who had no medical diseases were analysed as idiopathic causes 159(85%), surgical causes 28(15%) such as a history of ovarian drilling (13 cases), a history of oophorectomy (3 cases) and laparoscopy for recurrent ovarian cystectomy (3 cases). In addition, 9 patients had undergone multiple intracytoplasmic sperm injection (ICSI) (more than three times) where some studies have indicated this as a risk for ovarian insufficiency in the future.

In this study, a comparison between cases with medical causes and non-medical causes for POF by using the student's t-test test in terms of ovarian markers (basal hormonal profile) and there was no statistical significance regarding (P value). Table 3 summarises the result.

By using the ANOVA test a comparison was made between common recorded medical diseases (DM, Hypothyroidism, Asthma, Endometriosis and Hyperprolactinemia) and the

Table 1: General Characteristics of POF patients.

Characteristics		Value
Age (y)		31.19±3.86 (17 to 39)
Infertility type	Primary	234 (66.9)
	Secondary	81 (23.1)
Parity	P1	59 (16.9)
	P2	19 (5.4)
	Multiparity	3 (0.9)
Abortion rate	A1	42 (12)
	Recurrent	36 (10)
Menstrual Cycle	Regular	248 (70.9)
	Irregular	102 (29.1)
Family history of POF	Positive	4 (1.1)

The values are presented either mean± SD (range) or number (%). P1: One Parity; P2: Two Parity; A1: One Abortion

Table 2: Medical diseases and POF cases.

Medical diseases (no. 167)	Value
DM	23(13.8%)
Endometriosis	12(7.2%)
Asthma	9(5.4%)
Skin disease	3(1.8%)
Thrombocytopenia	2(1.2%)
Ceiliac Disease	1(0.6%)
HBV	1(0.6%)
SLE	1(0.6%)
Vitilligo	1(0.6%)
Hyperprolactenemia	50(29.9%)
Hypothyrodism	52(31.1%)
Hyperprolactenemia and Hypothyrodism	12(7.2%)

The values are presented as number (%)
DM: Diabetes Mellitus; SLE: Systemic Lupus Erythematosus

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sensitivity of ovarian markers (AFC, FSH, AMH). It was found that FSH was the most sensitive in comparison with AFC and AMH and the three ovarian markers that were only statistically significant in cases with Hypothyroidism as well as Hyperprolactinemia. Tables 4,5 summarise the result.

In addition, by using the Fisher (LSD) test, the sensitivity level of FSH to predict future ovarian failure among cases with common medical diseases (Hypothyroidism as well as Hyperprolactinemia) was analysed. The result showed that Hypothyroidism (14.78±12.87) indicates statistically significant differences. This indicates that cases with hypothyroidism with FSH level 14.78±12.87 would be predicted to be highly likely to develop ovarian failure Table 6 Figure 1.

Discussion

POF is one of the common problems among young women, possibly leading to future infertility. Therefore, it is important to search for the causes of POF and to treat it early in order to reduce the possibility of ovarian tissue damage [14]. The

Table 3: Comparison of ovarian markers between medical diseases and non-medical diseases.

	No diseases Mean ±SD	Diseases Mean ±SD	t	P
AFC	3.89±3.07	3.44±3.00	-0.675	0.50
FSH	11.8±9.54	10.21±9.68	-1.080	0.28
AMH	0.69±0.56	0.68±0.50	-0.124	0.90

SD: Standard Deviation; t: Student's t-test; P: P value
AFC: Anra-Follicl Count; FSH: Follicular Stimulating Hormone; AMH: Anti-Mullarian Hormone

Table 4: Comparison of ovarian markers among Diabetic, Asmthic, Endometriosis (shows most sensitive indicator for ovarian insufficiency).

	F	P
AFC	0.410	0.746
FSH	0.677	0.566
AMH	0.276	0.842

F: ANOVA test; P: P value

Table 5: Comparison of ovarian markers among Hypothyroidism and Hyperprolactinemia (shows most sensitive indicator for ovarian insufficiency).

	F[a]	P
AFC	0.173	0.914
FSH	2.858	0.037*
AMH	1.055	0.369

[a]ANOVA test
*Significant $P<0.05$

Table 6: Comparison of FSH between normal and hormonal disturbance patients.

	Hormonal State			
	No medical disease (normal)	Hyperprolac	Hypothyro	Hyperprolac & Hypothyro
FSH	10.7±8.71[a]	11.37±8.99	14.78±12.87[a]	14.43±8.18

[a]indicates statistically significant differences ($P \leq 0.05$).
The values are presented as mean±SD

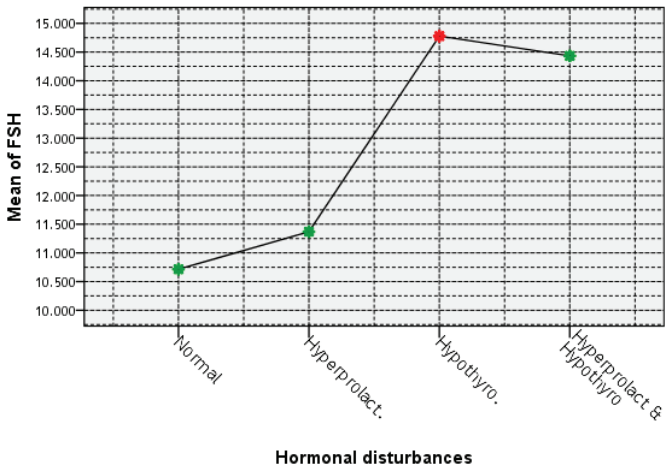

Figure 1: Comparison of FSH between different hormonal disturbance patients.

relation between the presence of other specific medical problems and the prediction of POF is still under research. The present study revealed that medical disorders were commonly seen among POF cases, with problems related to the thyroid gland, pituitary problems and diabetes mellitus being the most common.

Generally, research reported that 20% to 30% of cases with POF were associated with autoimmune diseases and endocrinopathies. Such medical problems include thyroid diseases, insulin dependent diabetes mellitus, polyglandular syndromes, rheumatoid disease, systemic lupus erythematosus, vitiligo, myasthenia gravis, and Crohn's disease [15]. Bidet et al., studied the association between POF and medical disorders among 357 women and found that about 14% of the cases had thyroid disorders [16]. In addition, a study by Goswami et al., in India found the prevalence of thyroid autoimmunity in 58 patients with POF which represented 24.1% of the patients [8,17]. However, with regard to the clinical or biochemical indicators for ovarian function, most research has not taken this into account and some studies have shown no significant importance as most of the POI patients were diagnosed late [9].

According to the result of this study and previous studies, all women with medical problems such as thyroid, diabetes mellitus and other abovementioned problems should be educated regarding the symptoms, investigation control and treatment by referring to an endocrinologist for further evaluation as well as long-term follow-up [18]. Therefore, the early diagnosis of medical disorders is very important for a young female for her future regarding the prevention of additional damaging processes for other vital organs including the ovaries.

This study suffers from some limitations involved in the endocrinological screening such as thyroid antibodies and ovarian autoantibodies. However, these tests could not be carried out due to its retrospective nature. Moreover, a randomised control trial (RCT) with a large sample of the population would be needed in order to evaluate the conception of POF among patients with several medical diseases.

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Conclusion

POF is usually related to various disorders ending in the loss of ovarian function. The present study has revealed that medical disorders were commonly seen among POF cases, with problems related to the thyroid gland, pituitary problems and diabetes mellitus being the most common. In addition, the most sensitive predictor for future POF for this group is the level of FSH as it is the first to be affected in comparison with other ovarian markers (AMH, AFC). Thus, screening for POF symptoms must be taken seriously as POF can be predicted in some situations. So it is recommended to use FSH as a screening test to predict POF and to provide specific treatment based on the aetiology of POI, as well as an understanding the mechanisms of the disease that may eventually support the development and improvement of treatment.

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