

Evaluation of Hormones and Trace Elements in Women with Unexplained Infertility

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Summary

This study aims to Evaluation of prolactin (PRL), thyroid stimulating hormone (TSH), luteinizing (LH)and Follicle stimulating hormone(FSH)and trace elements (iron and copper) in women with unexplained infertility (UI). 60 women with unexplained infertility as well as (40) women with polycystic ovarian syndrome (PCOS) aged (20-35) year were included in this study. The women were divided according the type of infertility into primary and secondary groups (1°UI, 2°UI, 1°PCO and 2°PCO) respectively. Fifty healthy fertile women with the same age were included in this study as a control group. The results showed a significant increase in serum of Prolactin, TSH, LH levels in the two groups of women with explained infertility (pcos) compared to control and the two groups of women with unexplained infertility. In contrast no significant differences in Prolactin, TSH, FSH and LH levels in women with unexplained infertility in comparison with the control.Serum levels of iron and copper significantly increase in unexplained infertility groups in comparison with women with explained infertility and control groups. This study concluded that is Prolactin, TSH and LH hormone are not associated statistically with unexplained female infertility. The increase in Cu and iron may have an important etiological role in the pathogenicity of unexplained infertility.

Keywords: Unexplained infertility, PCOS, Hormone, Trace elements, Iron, Copper

Introduction

Infertility is defined as the inability to conceive naturally after one year of regular unprotected intercourse. Most of the time, infertility is some degree of subfertility in which 1 in 7 couples need specialist help to conceive. Subfertility can be either primary or secondary.¹ Infertility of unknown origin comprises both idiopathic and unexplained infertility.^(2,3) Most of the infertile couples have one of these three major causes including a male factor, ovulatory dysfunction, or tubal-peritoneal disease.⁽⁴⁾ According to the Center of Disease Control (CDC, 2013),⁽⁵⁾ the causes of female infertility can be divided into three broad categories including defective ovulation, transport and implantation.⁽⁶⁾ Unexplained infertility is one of the controversial subjects in infertility on which agreement is rarely found among practitioners. It is a term used to define 30–40 % of couples in whom standard investigations including semen analysis, tests of ovulation and tubal patency have failed to detect any gross abnormality.⁽³⁾ Couples with unexplained infertility suffer from both diminished and delayed fecundity.⁽⁷⁾

The diagnosis of unexplained infertility may be frustrating because if there is no explanation for infertility, there is no effective treatment.⁽⁷⁾ The prognosis is worse if the duration of infertility exceeds 3 years and female partner is > 35 years of age.⁽⁸⁾ Treatment has been indicated if the duration is more than 2 years or the female partner is > 35 years of age.^(8,9) Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism, chronic anovulation and polycystic ovaries.^(10, 11) The prevalence of classical forms of PCOS is from 6-9 to 19.9% and is even higher in women with menstrual disorders (17.4-46.4%), hyperandrogenism (72.1-82.0%), and anovulatory infertility (55-91%).^(12,13) Clinical symptoms include ovulatory dysfunction, hyperandrogenism, and polycystic ovaries. Metabolic disorders (obesity, insulin resistance, impaired glucose tolerance, type II diabetes mellitus, and dyslipidemia) are typical of 40-85% women with PCOS.⁽¹⁴⁾ Hormones from pituitary gland like TSH, prolactin or growth hormone may act synergistically with FSH and LH to enhance the entry of non-growing follicles into growth phase. In addition to this, thyroid hormones may

be necessary for maximum production of both estradiol and progesterone. ⁽¹⁵⁾

It is well known that the function of the thyroid hormones includes modulation of carbohydrates, proteins and fat metabolism, gene expression and also sexual and reproductive function and when the thyroid hormone gets out of balance, many body functions are affected. ⁽¹⁶⁾ Thyroid dysfunction in females have been found to be associated with anovulatory cycles, decreased fecundity and increased morbidity during pregnancy. ⁽¹⁷⁾

Hyperprolactinemia also adversely affects the fertility potential by impairing the pulsatile secretion of GnRH and hence interfering with ovulation. ⁽¹⁸⁾ Moreover it is associated with menstrual as well as ovulatory dysfunctions like amenorrhoea, oligomenorrhoea, anovulation, inadequate corpus luteal phase and galactorrhoea. ⁽¹⁹⁾

Hyperprolactinaemia results in inhibition of gonadotrophin releasing hormone (GnRH) release pulsatility from the hypothalamus and subsequent inhibition of LH and follicle stimulating hormone, ^(20, 21) leading to inhibition of ovarian function. Chronic increases in 17 β -estradiol also

stimulate prolactin secretion, both through actions on the pituitary gland and through hypothalamic mechanisms. ⁽²²⁾ High levels of circulating PRL, in physiology and pathological situations, are known to cause infertility. ⁽²¹⁾

Hypothyroidism can affect fertility due to anovulatory cycles, luteal phase defects, hyperprolactinemia and sex hormone imbalance. ⁽¹⁷⁾ Thyroid dysfunction is a condition known to reduce the likelihood of pregnancy and to adversely affect pregnancy outcome.

Abnormal patterns of gonadotropin secretion, including increased serum luteinizing hormone (LH) concentrations, low-normal follicle-stimulating hormone (FSH) levels, and increased LH/FSH ratios have long been recognized as common characteristics of women with PCOS. ⁽²³⁾

Trace elements play a vital role in many different biological functions. The relationship of trace elements to different disease states has long been known. ⁽²⁴⁾ Although trace elements are essential components of biological structures or essential for enzymatic function, they can be toxic at higher concentrations beyond what is necessary for their biological

functions.⁽²⁵⁾ Nutritional elements such as Zn, Cu, and Se are components of proteins, enzymes and hormones, which regulate many processes, including balancing redox reactions, immune response, and formation of connective tissue during development.⁽²⁶⁾

Iron is an element essential for life and maintaining normal organism function. It is also necessary for the production of myoglobin, oxidative phosphorylation within mitochondria, DNA synthesis.⁽²⁷⁾ Copper is normally bound to proteins as an essential enzymatic component. In terms of storage capacity, high concentrations of Cu are found in liver, which is the central organ for Cu homeostasis.⁽²⁸⁾ Other organs that have high concentrations of Cu are the brain, heart, stomach and intestine. Free Cu⁺ is a potent oxidant causing the generation of ROS in cells. Thus, the tight regulation of Cu homeostasis is required to maintain Cu uptake,

transport, storage, and excretion activities.⁽²⁹⁾

Patients and Method

This study has been conducted at AL-Hussein Teaching Hospital in Thi-Qar, Biochemistry Laboratory in College of Science, at the period between 10/8/2016 to 25/5/2017. Informed consent was obtained verbally from all participants. A total of one hundred women with infertility of the ages 20 – 35 years. The women are already diagnosed as infertile women by the consultant medical staff, according to clinical examination and symptoms. To compare the results, fifty healthy age matched females with a history of at least one child birth were also enrolled. The present study included (150) females, which divided into two general groups:

1. Control group: included (50) apparently healthy Fertile women.
2. Case group: included (100) infertile women

Table(1).Details of numbers and age of the studied groups

Groups	No.	Rang of Age (year)
Patients (infertile women)	100	20- 35
Control (fertile women)	50	20-35
Total	150	20-35

Also the women in this study were divided into subgroups according to type of infertility of infertile women showed as followings:

- 1- (1°UI): included (30) woman with primary unexplained infertile women.
- 2- (2° UI): included (30) woman with secondary unexplained infertile women.
- 3- (1°PCO): included (20) woman with primary explained infertile women (PCOS).
- 4- (2°PCO): included(20) woman with secondary explained infertile women (PCOS).

Specimen collection

About (5mL) of blood samples was collected by vein puncture using a sterile disposable syringe in plain plastic tubes. The serum was separated immediately in order to allow clotting at room temperature. The blood was centrifuged at 3000 revolution per minute (rpm) for 10 minutes and stored in plain tubes at (-20°C) until used or immediately analysed.

Determination of Serum Hormones

The Hormones (PRL, TSH, FSH, and LH) are a Full automated quantitative test for use with Autoanalyzer Cobas e411 instruments were used for the determination of (PRL TSH, FSH, and LH) in human serum or plasma using Elecsys and Cobas e immunoassay analyzers.

Determination of Serum Trace Element Concentration

Serum iron concentration was measured according to the method of iron kit. The used reagents were supplied by (Randox, UK).Serum Cu concentration was measured according to the method of copper kit (Spectrum, Germany).

Statistical Analysis

The Statistical Analysis System- SAS (2012) program was used to effect of difference factors in study parameters. Least significant difference – LSD test was used to significant compare between means in this study.

Result and Discussion

The women with primary and secondary unexplained infertility (UI) had the mean age of 29.25 ± 6.26 and 33.69 ± 6.36 years respectively, and the mean age of women with primary and secondary explained infertility (PCOS) groups were 25.844 ± 4.47 and 28.44 ± 4.21 years respectively. The mean age of the control group was 32.28 ± 6.70 years. The women with primary and secondary (UI) had the mean BMI values of 26.44 ± 3.24 and 27.27 ± 4.04 kg/m² respectively, and the mean BMI values of women with primary and secondary (PCOS) were 30.77 ± 3.11 and 31.34 ± 4.12 kg/m² respectively. The mean BMI value of control group was 26.02 ± 6.96 kg/m².

Serum Hormones Concentration

Table (2) shows no significant differences in Prolactin, TSH, FSH and LH levels in the two groups of women with (1°UI) and (2°UI) in comparison with the control group. These results are in agreement with Beyazit *et al.* 2016 and Verit *et al.*, 2017.^(30, 31) Also the study found no significant differences in such hormones levels between the two groups of the women with UI, can be observed.

The same table shows a significant increase in Prolactin, TSH and LH hormone levels in the two groups of women with explained infertility (1°PCO) and (2°PCO) in comparison with the control group ($p \leq 0.05$). These results agree with the results reported by George and Malini 2014 ; Shah *et al.* 2017.^(32, 33) The current study shows a significant increase in Prolactin, TSH and LH hormone levels in the two groups of women with (PCOS) in comparison with the two groups of women with (UI) respectively ($p \leq 0.05$). This result agrees with the study of Diamond *et al.* 2017,⁽³⁴⁾ while there are no significant differences in Prolactin, TSH and LH hormone levels between the two groups of the women with explained infertility (PCOS). These results are matched with the results of the study of Spandana *et al.* 2017.⁽³⁵⁾

However the results showed no significant differences in FSH hormone levels in the two groups of the women with PCO in comparison with the control group. it is no significant differences in FSH hormone levels between the two groups of the women with explained infertility (1°PCO) and (2°PCO) in comparison with the two groups of the women with unexplained infertility (1°UI) and (2°UI) respectively. These results agree with the two studies of Beyazit *et al.* 2016 and Mohammed *et al.* 2016.^(30, 36)

Also, no significant differences in FSH hormone levels between the two groups of women with (PCOS) can be observed.

The high prolactin, TSH and LH levels were found in PCOS women in the present study. Hyperprolactinemia can cause symptoms similar to PCOS. Reports have suggested that women with PCOS have elevated prolactin levels. This increased prolactin may augment by the inhibition of 3beta-hydroxysteroid dehydrogenase activity or, less often, through selective action on the sulfation of DHEA in adrenal or extra-adrenal sites. ⁽³²⁾

In many infertility cases, the diagnosis is simply unexplained because a variety of reasons like lack of ovulation, mechanical stoppage and parental age etc. ⁽³⁷⁾ hypothyroidism is defined by high TSH and normal thyroid hormones. ^(38,39) Hypothyroidism is one of the causes of ovulation dysfunction in women, resulting in infertility. ⁽⁴⁰⁾ The ovulation can be affected by hormonal imbalance, thyroid disorders or chronic diseases such as diabetes. ⁽⁴¹⁾ Some women with hyperprolactinemia might have primary hypothyroidism.

Abnormality of the hypothalamic-pituitary ovarian or adrenal axis has been implicated in PCOS. Disturbance in the pulsatility of gonadotrophin releasing hormone (GnRH) results in the relative increase in LH to FSH release. An abnormal feedback mechanism by ovarian estrogen is blamed to play role in this discriminated increase in LH release. ^(42, 35)

Table (2):-Serum Hormones levels of control and infertile groups

Groups	NO.	PRL (μ U/ml)	TSH (μ U/ml)	LH (μ U/ml)	FSH(μ U/ml)
Control	50	14.5 \pm 3.9 ^b	2.3 \pm 0.7 ^b	3.2 \pm 0.9 ^{bc}	5.4 \pm 1.4 ^a
1° UI	30	14.5 \pm 2.9 ^b	2.3 \pm 0.7 ^b	2.6 \pm 0.7 ^c	5.3 \pm 1.2 ^a
2° UI	30	14.4 \pm 2.9 ^b	2.1 \pm 0.6 ^b	3.6 \pm 1.0 ^b	5.4 \pm 1.4 ^a
1° (PCO)	20	16.3 \pm 3.0 ^a	2.8 \pm 0.7 ^a	8.1 \pm 1.8 ^a	5.3 \pm 1.3 ^a
2° (PCO)	20	16.1 \pm 3.0 ^a	2.9 \pm 0.8 ^a	8.0 \pm 1.7 ^a	5.4 \pm 1.4 ^a

-Each value represents mean \pm S.D values with non-identical superscript (a, b or c ...etc.) were considered significantly differences ($P \leq 0.05$). **Control:** fertile woman, **1°UI:** Primary unexplained infertility, **2°UI:** Secondary unexplained infertility, **1°PCO:** Primary explained infertility, **2°PCO:** Secondary explained infertility, **No:** Number of subjects, **SD:** Standard deviation, **LSD:**Least Significant Difference.

Serum Trace Elements Concentration

Table (3) shows a significant increase in the concentration of serum Fe in the two groups of the women with unexplained infertility (1°UI) and (2°UI) in comparison with control group ($p \leq 0.05$). Also, it is found a significant increase in the concentration of serum Fe in (1°UI) in comparison with (2°UI), (1°PCOS) and (2°PCO) groups respectively ($p \leq 0.05$), but there are no significant differences in the concentration of serum Fe between (2°UI), (1°PCOS) and (2°PCO) groups respectively ($p \leq 0.05$). The same Table shows no significant differences in the concentration of serum Fe in the two groups of women with explained infertility (1°PCOS) and (2°PCO) in comparison with control group ($p \leq 0.05$).

Table (3) shows a significant increase in the concentration of serum Cu in the two groups of the women with unexplained infertility (1° UI) and (2° UI) in comparison with control group ($p \leq 0.05$). Also it is a significant increase in the concentration of serum Cu in the two groups of women with unexplained infertility (1°UI) and (2°UI) in comparison with two groups of the women with explained infertility (1°PCO) and (2°PCO) respectively ($p \leq 0.05$). While there are no significant differences in the concentration of serum Cu between the two groups of women with unexplained infertility ($p \leq 0.05$).

The same Table shows a significant increase in the concentration of serum Cu in two groups of the women with explained infertility (1°PCO) and (2°PCO) groups in comparison with control group ($p \leq 0.05$). But no significant differences in the concentration of serum Cu (1°PCO) and (2°PCO) groups ($p \leq 0.05$), can be observed.

This study shows a significant increase in the concentration of serum Fe in two groups of women with unexplained infertility (1°UI) and (2°UI) in comparison with fertile women. Also, there are a significant increase in the levels of serum Fe in (1°UI) in comparison (2°UI), (1°PCOS) and (2°PCO) groups respectively ($p \leq 0.05$). This result disagreement with the study of Alwais *et al.* 2016.⁽⁴³⁾

There are no significant differences in the concentration of serum Fe between (2°UI), (1°PCOS) and (2°PCO) in comparison with fertile women. This result matched with the results study of Alwais *et al.* 2016.⁽⁴³⁾ The non-significant differences in the concentration of serum iron between two groups of women with explained infertility (1°PCOS) and (2°PCO) in comparison with fertile women. This result matched with the results study of Li *et al.*, 2016.^(44, 45)

In this study it is found high concentration of serum iron in women with unexplained infertility. There are few studies investigated the effect of iron overload (toxicity) and fertility and even less with regard to female fertility. However, there is a link between iron overload and female infertility.⁽⁴⁶⁾ Excess iron leads to reduced production of the hormones LH and FSH from the anterior pituitary suggesting impaired oocyte maturation and low ovarian reserve.⁽⁴⁷⁾ In this study, no significant differences in serum levels of iron and were observed between the two groups of the women with (PCOS) and control group. A research conducted by Taghavi *et al.* in 2009 in Iran on 50 PCOS patients without overweight did not show iron overload in these patients.⁽⁴⁸⁾ A cross-sectional study of Lim *et al.* on 578 people in 2016 indicated that the serum levels of iron had no difference between the two PCOS and non-PCOS groups.⁽⁴⁴⁾

In this study the high concentration of serum Cu in the women with unexplained infertility reported by the current study matched with the results of study of AL-Saraf *et al.*, 2005,⁽⁴⁹⁾ but disagreement with results of study of Bawa and Tyagi who suggest the copper lower in the women with primary and secondary unexplained infertility than in control subjects and suggest that hypocupraemia may be a factor in the aetiology of infertility in these women.⁽⁵⁰⁾ Whereas the reported significant increase in the concentration of serum Cu in two groups of women with explained infertility in comparison with fertile women, matched with the results of studies of Kurdoglu *et al.*, 2012 and Muyan, 2016.^(51, 52) but disagreement with the results of study of Bawa and Tyagi who suggest the copper lower in the women with primary and secondary explained infertility than in control subjects.⁽⁵⁰⁾ The elevation in serum copper levels may directly affect infertility rates by lowering progesterone levels resulting in annovulation, implantation failure or luteal phase deficits.⁽⁵³⁾ Copper has also been shown to block the absorption of many essential minerals directly involved with reproductive pathways, especially zinc.⁽⁵⁴⁾

In this work there were high levels of serum Cu concentration in women with (PCOS) in comparison with fertile women. The PCOS patients also had a statistically and significantly higher amount of copper than the control group.⁽⁵²⁾ The survey conducted by Celik on copper, homocysteine, and early vascular disease in lean women with PCOS showed high copper levels in PCOS patients.⁽⁵⁵⁾ A similar result was obtained by a study on mice.⁽⁵⁶⁾ Previous studies have shown that patients with PCOS Copper is involved in the metabolism of oxygen and plays an important role in free radical reactions.^(57, 52, 58)

Table (3):-Serum trace elements levels of control and infertile groups

Groups	NO.	Fe (mg/dl) mean± SD	Cu (mg/dl) mean± SD
Control	50	82.55± 15.79 ^c	105.11±21.38 ^c
1° UI	30	125.01 ± 24.28 ^a	188.06±56.40 ^a
2° UI	30	114.69 ±26.36 ^b	175.24±43.00 ^a
1° PCO	20	84.03 ± 5.65 ^c	121.41±17.52 ^b
2° PCO	20	84.30 ±7.64 ^c	120.15±15.93 ^b
LSD		7.66	14.43

- Legend as in Table (2)

Conclusion

This study concluded that is Prolactin, TSH and LH hormone are not associated with unexplained female infertility. The increase in Cu and iron may have an important etiological role in the pathogenicity of unexplained female infertility.

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تقدير الهرمونات والعناصر النادرة لدى النساء المصابات بالعقم غير المفسر

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الخلاصة

تهدف هذه الدراسة إلى تقييم هرمون الحليب (PRL)، هرمون تحفيز الغدة الدرقية (TSH)، هرمون التبييض (LH) وهرمون التحفيز الجريبي (FSH). إضافة إلى تقييم العناصر النادرة (الحديد والنحاس) في النساء المصابات بالعقم غير المفسر (UI). تم تضمين 60 امرأة مصابة بالعقم غير مفسر وكذلك (40) امرأة مصابة بمتلازمة تكيس المبايض (PCOS) في هذه الدراسة واللواتي تتراوح أعمارهن بين (20-35) سنة. تم تقسيم النساء العقيمات وفقاً لنوع العقم إلى مجموعة عقم أولي و مجموعة عقم ثانوي (2°PCO , 1°PCO). كذلك تضمنت الدراسة خمسين امرأة خصبه صحيحة بنفس عمر النساء العقيمات كمجموعة سيطرة. بينت النتائج وجود زيادة معنوية في مستوى الهرمونات (LH, TSH, PRL) في مجموعتي النساء اللواتي يعانين من عقم (PCOS) مقارنة بمجموعة السيطرة ومجموعتي النساء اللواتي يعانين من العقم غير المفسر. في المقابل لا توجد فروقات معنوية في (LH, TSH, PRL) في النساء ذوات العقم غير المفسر بالمقارنة مع مجموعة السيطرة. كما بينت النتائج ان هناك زيادة معنوية في مستويات الحديد والنحاس في مجموعتي العقم غير المفسر بالمقارنة مع مجموعة السيطرة والنساء ذوات العقم المفسر. وخلصت هذه الدراسة إلى أن هرمونات (PRL, TSH, LH, FSH) لا تشترك باحداث مرض العقم غير المفسر لدى النساء. الزيادة في مستويات الحديد والنحاس قد يكون لها دور مسبب مهم في احداث مرض العقم غير المفسر لدى النساء.