

EVALUATION THE EFFECT OF METFORMIN ON HORMONES SERUM LEVELS IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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Abstract

Background: Polycystic ovary syndrome [PCOS] is a common disease that affected the reproductive problem. **Aim:** the study tried to determine the association between PCOS with the body mass index (BMI) and the effect of metformin as treatment for PCOS.

Patients and Methods: This case control prospective experimental study was carried out in Kirkuk General Hospital from January 2014 to July 2014. The recruited cases divided into three groups; Group I, 68 women with normal menstrual cycle as control group; Group II, 61 cases diagnosed as a PCOS; and Group III :- 30 cases selected from group two to receive treatment with Metformin to determine the effect of the treatment on different variables. **Results:** The highest percentage of PCOS (36.1%) was found in those with age group between (20-25) years. Most (65.6%) of PCOS subjects were with overweight or obese. BMI mean value was (28.92±6.68) in women with PCOS, while in control the corresponding value was (25.09±4.35). FSH, and testosterone were significantly higher in women with PCOS than in control. Metformin reduced serum FSH, LH, prolactin and testosterone, with non-significant difference. **Conclusion:** PCOS is independently associated with elevated BMI. Metformin treatment of PCOS induced t reduction in serum testosterone and FSH, LH and serum prolactin but not reach significant level. This warranted performance a large scale clinical trial to evaluate the therapeutic effect of metformin alone or in combination with diet control approach for treatment of PCOS. These findings have implications for the pathophysiology of obesity development and management in PCOS.

Keyword: PCOS, Metformin, FSH, LH, Prolactin, Testosterone.

Introduction

Polycystic ovary syndrome (PCOS) is the most hormonal disorder among women of reproductive age and associated with infertility.[1] The etiology of the syndrome include combination of genetic and environmental factors.[2-5] Management of the syndrome is essential since it is associated with social impact and affect the quality of life.[6] Teede et al[7] proposed that there is a bidirectional interaction between PCOS and weight with PCOS driving weight gain and weight gain contributing to an increased prevalence and severity of polycystic ovary syndrome.

Metformin is one of the treatment for PCOS and previous researches [8-11] suggest its therapeutic effect in control of the syndrome. Thus this study performed in order to evaluate the therapeutic effect of metformin as treatment for PCOS. The study was approved by the ethical committee of Tikrit University College of Medicine.

Materials and methods

This case control prospective experimental study was carried out in Kirkuk General Hospital from January 2014 to July 2014. The recruited cases divided into three groups as:

1. Group I :- 68 cases with normal menstrual cycle women volunteers who freely agreed to participate in the study the mean age was 29.24 year, regarded as control group.
2. Group II :- 61 cases diagnosed as a Poly cystic ovarian Syndrome women ,the mean age was 25.59

year , regarded as a pathological group before treatment with metformin.

3. Group III :- 30 cases selected from group two to receive treatment with Metformin [500 mg twice daily (Glucophage ® MERK- SERONA)] to determine the effect of the treatment on different variables.

The serum of patient was collected after an overnight fast of 10 -12 h, separated after centrifugation into two parts. The blood samples were centrifuged at 3000 rpm for 5 minutes, it was essential to ensure that the serum did not hemolysis. The clean serums were transferred to clean plastic tubes by micropipette. The tubes were topped by plastic stoppers and stored at - 20⁰ C in order to avoid variation, till the time of analysis .The obtained serum was used for the estimation of serum FSH, serum LH, serum Prolactin, serum testosterone. In all tests internal quality control tests was performed to detect the accuracy of the results

Age Distribution: Patients and controls age distribution is presented in table 1.The highest percentage of disease (36.1%) was found in those with age group between (20-25) years, while lowest percentage of disease (9.8%) was found in age group of (38-43) years.In control, also the highest percentage (27.9%) was found in age group of (26-31) years and lowest percentage (14.7%) was found in age group of (38-43) years.

Table 1: Age frequency of the PCOS patients and controls

Age	PCOS patients No (%)	Controls
Mean \pm SD	26.1 \pm 7.3	28.2 \pm 7.4
(14-19)	7 (11.5%)	14 (20.6%)
(20-25)	22 (36.1%)	10 (14.7%)
(26-31)	10 (16.4%)	19 (27.9%)
(32-37)	16 (26.2%)	15 (22.1%)
(38-43)	6 (9.8%)	10 (14.7%)
Total	61 (100%)	68 (100%)

Body Mass Index (BMI): Table 2 shows the distribution of patients and controls according to BMI. Both patients and control groups was divided into four groups according to BMI. In patients group the highest percentage (41%) was found in obesity

group (BMI>30) and lowest percentage (24.6%) was found in age group of (25 -29.99). In controls also the highest percentage (55.9%) was found in age group of (25 - 29.99) and lowest percentage (7.4%) was found in obesity group (BMI>30).

Table 2. Body mass index frequency of the PCOS patients and controls:

BMI (Kg/m ²)	PCOS patients	Control
Underweight < 18.5		10 (14.7%)
Normal weight (18.5-24.99)	21 (34.4%)	15 (22%)
Over weight (25-29.99)	15 (24.6%)	38 (55.9%)
Obese > 30	25 (41%)	5 (7.4%)
Total	61 (100%)	68 (100%)

Mean value and SD of BMI and Age in women with PCOS compared to control.

BMI mean value was (28.92 \pm 7.73) in women with PCOS, while in control the corresponding value as (25.08 \pm 4.35), the difference between two groups was

significant (p = 0.04), on the other hand the mean value of age was (27.50 \pm 7.25) in women with PCOS, while in control the mean value was (29.23 \pm 7.15), the difference between two groups was non-significant (p >0.05) table 3.

Table 3. Mean value and SD of BMI and Age in women with PCOS compared to control.

	Patient		Control		P value
	Number	Mean \pm SD	Number	Mean \pm SD	
BMI (Kg/m ²)	61	28.92 \pm 7.73	68	25.09 \pm 4.35	0.04
Age (years)	61	27.5 \pm 7.25	68	29.23 \pm 7.15	NS

Mean value and SD of hormones in women with PCOS compared to control.

Serum FSH mean value was (8.26 \pm 3.73) mIU/ml in women with PCOS, While in control the corresponding value was (6.54 \pm 1.82) mIU/ml. The difference between the two groups was significant (p = 0.04) Table 4. In addition serum LH mean value was non-significantly difference (p>0.05) (7.58 \pm 4.51) mIU/ml in women with PCOS as compared to control (5.56 \pm 1.25) mIU/ml. Where as serum prolactin mean value was non-significant (21.15 \pm 8.16)mIU/ml compared to control (22.0 \pm 8.75)mIU/ml, Serum testosterone mean value was (0.72 \pm 0.57)ng/ml in women with PCOS, While in control the corresponding value was (0.41 \pm 0.19) ng/ml. The difference between two groups was significant (p = 0.01).

Mean and SD of hormones in women with PCOS before and after treatment with metformin.

FSH serum mean value was (8.26 \pm 3.7) mIU/ml in women with PCOS before treatment with metformin, While after treatment the serum mean value was (6.79 \pm 2.47) mIU/ml. The difference between two groups was non-significant (p >0.05). LH serum mean value was (6.58 \pm 4.35) mIU/ml in women with PCOS before treatment with metformin, While after treatment the serum mean value was (5.91 \pm 3.22) mIU/ml. The difference between two groups was non-significant (p >0.05). Prolactin serum mean value was (19.5 \pm 9.03) ng/ml in women with PCOS before treatment with metformin, While the serum mean value was (16.86 \pm 6.57) ng/ml. The difference between two groups was non-significant (p >0.05). Testosterone serum mean value was (0.78 \pm 0.64) ng/ml in women with PCOS before treatment with metformin, While the serum mean value (0.51 \pm 0.32) ng/ml after treatment with metformin. The difference between two groups was non-significant (p >0.05), table 5.

Table 4. Mean value and SD of hormones in women with PCOS compared to control.

Hormones	Patient Mean \pm SD	Control Mean \pm SD	P value
FSH mlU/L	8.26 \pm 3.73	6.54 \pm 1.82	0.04
LH mlU/L	7.58 \pm 4.51	5.56 \pm 1.25	NS
Prolactin ng/ml	21.15 \pm 8.16	22.0 \pm 8.75	NS
Testosterone ng/ml	0.72 \pm 0.57	0.41 \pm 0.19	0.01

Table 5. Mean and SD of hormones in women with PCOS before and after treatment with metformin

Hormones	Before treatment Mean \pm SD	After treatment Mean \pm SD	P value
FSH mlU/L	8.26 \pm 3.73	6.79 \pm 2.47	NS
LH mlU/L	6.58 \pm 4.35	5.91 \pm 3.22	NS
Prolactin ng/ml	19.5 \pm 9.03	16.86 \pm 6.57	NS
Testosterone ng/ml	0.78 \pm 0.64	0.51 \pm 0.32	NS

Discussion

The present study indicated that polycystic ovary syndrome was common in the age group of 20 to 25 years (36.1%), followed by the age of 32 to 37 years (26.2%). This finding suggest that PCOS was linked to women age of hormonal activity (20-25years) and the age of premenopausal, both periods that may be associated with hormonal instability. The mean age of this study was 26.1 years which is lower than that of control group (28.2 years) and this mean was in agreement to that reported by others.[12,13] However, these two studies reported a higher mean age for women with PCOS than that of the present study. The variation in mean age between this and other studies may be due to differences in study design, study population, genetic and environmental factors.

Women with polycystic ovary syndrome in this cohort study are overweight (24.6%) or obese (41%), however, 34.4% had a normal BMI. In the present study frequency of normal BMI in women with PCOS was about similar to that reported by Moran et al[12] and lower than reported by Saxsena et al.[13] Furthermore, this study confirm the previous reports of high prevalence of overweight and obesity in women with PCOS.[7,12,13,14,15] Thus this study finding confirm that PCOS indently associated with abnormal BMI.[7,12,13] The present study indicated that there was significant increase in mean serum level of FSH in women with PCOS compared to control .This finding was not in agreement with Johanna et al[16] who demonstrated that FSH levels are lower in infertile women with PCOS women.

In addition, this study shows that there was a non-significant increase in mean serum level of LH in women with PCOS compared to control .This result was in agreement to Lavanya et al [17] study in which they reported that only 17-18 % of PCOS patients had elevated LH levels There are also number of other disorders that may result in ovulatory dysfunction, including hyper prolactinemia. The results of present study also showed that the mean levels of prolactin did not differ significantly between

all groups enrolled in this study .In contrast to Robinson et al [18] report who found mild elevation in prolactin levels in women with PCOS.

Women with PCOS were with significantly (P= 0.01) higher serum testosterone mean value than in control. Women with PCOS have high total and bioavailable testosterone and irregular periods and often do not ovulate. They also have extra hair growth on their face and acne. This is quite a common condition that is often associated with being overweight and insulin resistance. In PCOS, cortisol secretion is mildly elevated. All of these abnormalities may predict a social impact and interfere with the quality of life of women with PCOS. Metformin was effective in reducing serum testosterone mean value in women PCOS as this study indicated. However, metformin reduced the mean serum value of LH, FSH and prolactin after treatment but not reach a significant level . The effect of metformin on androgen production has been controversial [8-11]. It may be argued that the metformin effect on circulating androgen is a byproduct of ovulation resumption .Further, it has been suggested that metformin reduces hyper androgenism through its effect on both the ovary and adrenal gland suppressing their androgen production ,reducing pituitary luteinizing hormone and increase the production of sex hormone binding globulin by the liver.[10]

Harborne and Colleagues, on the other hand, reported no significant change in androgen or sex hormone binding globulin levels in hirsute patients treated with metformin [11] .

In conclusion, PCOS is independently associated with elevated BMI. Metformin treatment of PCOS induced significant reduction in serum FSH, Testosterone, LH and serum prolactin, but not reach significant levels in our study cohort. This warranted performance a large scale clinical trial to evaluate the therapeutic effect of metformin alone or in combination with diet control approach for treatment of PCOS. These findings have implications for the pathophysiology of obesity development and management in PCOS.

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تقييم تأثير علاج المتفورمين علي مستويات الهرمونات في مصل النساء المصابات بمتلازمة تعدد الاكياس في المبيض

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الملخص

متلازمة تعدد الاكياس في المبيض هي من اكثر الامراض شيوعا التي تؤثر على مستوى الانجاب المشتركة مع التأثير الاجتماعي والصحي. **الهدف من الدراسة:** هدفت الدراسة التي أجريت لتحديد العلاقة بين مؤشر كتلة الجسم ومتلازمة تعدد الاكياس في المبيض والأثر العلاجي للمتفورمين.

طريقة العمل: أجريت الدراسة التجريبية المحتملة لهذه الحالة في مستشفى كركوك العام في الفترة من كانون الثاني/ 2014 إلى تموز/ 2014. وتنقسم الحالات المعينة إلى ثلاث مجموعات؛ المجموعة الأولى ثمانية وستون من النساء السليمات ظاهريا من خلال الدورة الحيضية المنتظمة كمجموعة سيطرة؛ المجموعة الثانية احدى وستون حالة تم تشخيصها بأنها من المصابات بمتلازمة تعدد الاكياس في المبيض؛ والمجموعة الثالثة:- ثلاثون حالة من المجموعة الثانية تتلقي العلاج مع المتفورمين لتحديد تأثيره على متغيرات مختلفة لدى النساء المصابات

النتائج: تم العثور علي اعلي نسبة مئوية من متلازمة تعدد الاكياس وهي (36.1 في المائة) في الفئات العمرية بين السنوات (20-25) سنة . كان معظمهم (65.6 في المائة) من النساء المصابات بفرط الوزن أو السمنة. وكانت القيمة المتوسطة لمؤشر كتلة الجسم (6.68 ± 28.92) في النساء ذوات متلازمة تعدد الاكياس في المبيض، بينما كانت في مجموعة السيطرة مؤشر كتلة الجسم (4.35 ± 25.09) . وكانت تراكيز هورمونات FSH, LH ، وهرمون التستوستيرون اعلي في النساء ذوات متلازمة تعدد الاكياس في المبيض من مجموعة السيطرة. وقد ادى علاج المتفورمين الى انخفاض في تراكيز هورمونات FSH, LH، وهرمون الحليب وهرمون التستوستيرون دون الوصول الى فارق معنوي.

الاستنتاجات: متلازمة تعدد الاكياس في المبيض ترتبط بشكل مستقل مع ارتفاع مؤشر كتلة الجسم. وعلاج المتفورمين لمتلازمة تعدد الاكياس في المبيض سبب انخفاضاً في هرمون التستوستيرون و FSH ، LH وهرمون الحليب ولكن ليس بشكل معنوي . وهذا ما يبرر الأداء على نطاق واسع التجربة السريرية لتقييم الأثر العلاجي للمتفورمين وحده أو بالاقتران مع اسلوب تحكم في النظام الغذائي لعلاج متلازمة تعدد الاكياس في المبيض. هذه النتائج لها اثارها علي الفسيولوجية المرضية لتقدم السمنة وعلاج متلازمة تعدد الاكياس في المبيض....