International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 09, 2020
ISSN: 1475-7192

The effect of folic acid on lipid peroxidation in women with polycystic ovary syndrome

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Abstract:

Introduction: *Polycystic ovary syndrome (PCOS) is one of the important causes of infertility Worldwide and affects about 20% of infertile couples. Women with PCOS have a surged risk of first trimester spontaneous abortion ranging from 25% to 73%. Oxidative stress has been linked to various disorders; including epilepsy, depression, ulcerative colitis and other diseases. However, it is still unknown whether it is a cause or a consequence in PCOS.* ***Aim of the study:*** *The aim of this study was to evaluate the effect of folic acid 5mg/daily on lipid peroxidation in adult females with polycystic ovary syndrome.* ***Methods:*** *The current study was carried out on 120 women in reproductive period, their ages ranged from 18 to 39 years. They were organized into three groups: group one studied 40 women having a PCOS treated with 5mg/day folic acid/day for 3 months, group two included 40 adult females without PCOS treated with 5mg/day folic acid/day for 3 months, And group 3 included 40 females with PCOS not treated with 5mg/day folic acid/day.* ***Results:*** *Folic acid administration at a daily dosage of 5 mg was found to reduce significantly the rate of lipid peroxidation byproduct, malondialdehyde (MDA) in PCOS women.* ***Conclusion:*** *It was clear that folic acid supplementation to PCOS women in a given pharmacological dose might have a positive effect on oxidative stress.*

Keywords*: folic acid , lipid peroxidation , polycystic ovary syndrome.*

I. Introduction

Polycystic ovarian syndrome (PCOS) is a multifactorial endocrine disorder predominantly affecting between 5%–10% of reproductive-aged women. PCOS women basically have clinical features of oligo- or an-ovulatory cycle, obesity, and hyperandrogenism [1] Moreover, PCOS can occur with hyperinsulinemia, glucose intolerance, hyperlipidemia, type 2 diabetes mellitus, hypertension, coronary atherosclerosis, and endometrial cancer [2–5].

Oxidative stress could be involved in the development of various diseases such as Alzheimer's

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Received: 10 Jan 2020 | Revised: 09 Feb 2020 | Accepted: 27 Mar 2020

disease, autism, atherosclerosis, diabetes, heart failure, and inflammation [6–12]. Oxidative stress refers to the imbalance between oxidants and antioxidants in favour of oxidants. This leads to the accumulation of peroxides and free radicals that can damage different components of the cell, including nucleic acids, proteins, lipids, carbohydrates, and other molecules [13,14] The two major forms of radicals are reactive oxygen species (ROS) and reactive nitrogen species (RNS). The ROSs refer to superoxide radical, hydrogen peroxide, and hydroxyl radical,15,16 and the RNS include nitric oxide and its metabolites [16]. MDA is a byproduct of lipid peroxidation which considered as a destructive peroxide to the cell components and one of the major parameters of oxidative insult. Oxidative stress has been associated with PCOS [18–21]. However, the exact mechanism of oxidative stress in the pathogenesis of PCOS is not yet fully understood. Studies have proposed that oxidative stress appears to be involved in PCOS by which contributes to increase androgen levels, disturbing follicular development, and infertility [22,23]

This study aimed to compare oxidative stress indices (MDA level) among women diagnosed with PCOS vs non-PCOS women.

II. Patients and methods

This is a randomized blind comparative study conducted on 120 women in the Department of Obstetrics & Gynecology at Alhindyya Hospital / Karbalaa city / Iraq. The study began on January 2018 and end in August 2019. Patients were assorted into three groups:

i. **Group 1:** Includes 40 women without PCOS, treated with 5mg/day folic acid/day for 3 months.

ii. **Group 2:** Includes 40 women with PCOS treated with folic acid 0.5mg/day.

iii. **Group 3:** Include 40 women with PCOS not treated with folic acid 0.5mg/day.

The inclusion criteria were:

i. Age between 19 and 39 years old.

ii. Patients with PCO (PCOS was diagnosed according to the Rotterdam criteria if at least two of the following criteria were present: Oligo/amenorrhea, clinical or biochemical hyperandrogenism and PCO on USG)

The exclusion criteria were:

a. Women with any systemic disease

b. Women have chromosomal, uterine abnormalities; antiphospholipid syndrome, Inflammatory, autoimmune and any other condition affecting homeostasis, will be ruled out by either physical examination or patient history.

c. Smokers and alcohol consumption.

d. Patient with prolactinoma, congenital adrenal hyperplasia, Cushing syndrome, Virilizing ovarian or adrenal tumors.

All patients were subjected to the following:

i. An informed consent obtained from all participants in this research.

ii. **Personal history:** Name, age, parity, occupation, residency and Special habits.

iii. **Husband history:** name, age, occupation, residency, Special habits and chronic diseases.

iv. **Past history:** medical diseases, abdominal surgeries, drug therapy or allergy.

v. **Menstrual history:** menarche, regularity, duration, amount and associated pain.

vi. **General & local clinical examination:** to exclude general diseases, local causes of RPL.

vii. Measurement of serum MDA level using TBARs method [24].

viii. Finally, using folic acid to evaluate its effect in prophylaxis against oxidative stress in women with polycystic ovary syndrome.

III. Results

The present work was carried out on 126 pregnant women in reproductive period, their age ranged from 19 to 39 years. They were assorted into two groups: Group one included 40 adult females having a PCOS with folic acid supplementation. Group II included 40 adult females having no PCOS without folic acid. And group 3 included 40 adult females with PCOS not treated with folic acid, 5mg / day for 3 months.

All participants completed the study and the primary outcome was analyzed. Both groups were well matched (Table 1) considering the age, gravidity, parity and BMI. However, MDA level in group 1and 3 was significantly higher than group 2:

Table 1 The clinical data and MDA level of the studied patients

	Group 1	**Group 2**	**Group 3**	***P value***
Age	26.77±3.53	24.69±4.66	26.31± 2.99	0.866
Gravidity	3.80±0.61	3.63±0.34	3.49 ± 0.77	0.866

Parity	0.43±0.48	0.41±0.39	0.43 ± 0.57	0.866
BMI	25.28±2.68	24.58±2.75	25.33 ± 2.19	0.866
MDA level	6.79±0.53	3.51 ± 0.77	7.97 ± 0.49	< 0.05

1- Effect of folic acid intake on MDA level in PCOS women with folic acid (group 1) and non-PCOS with folic acid (group 2).

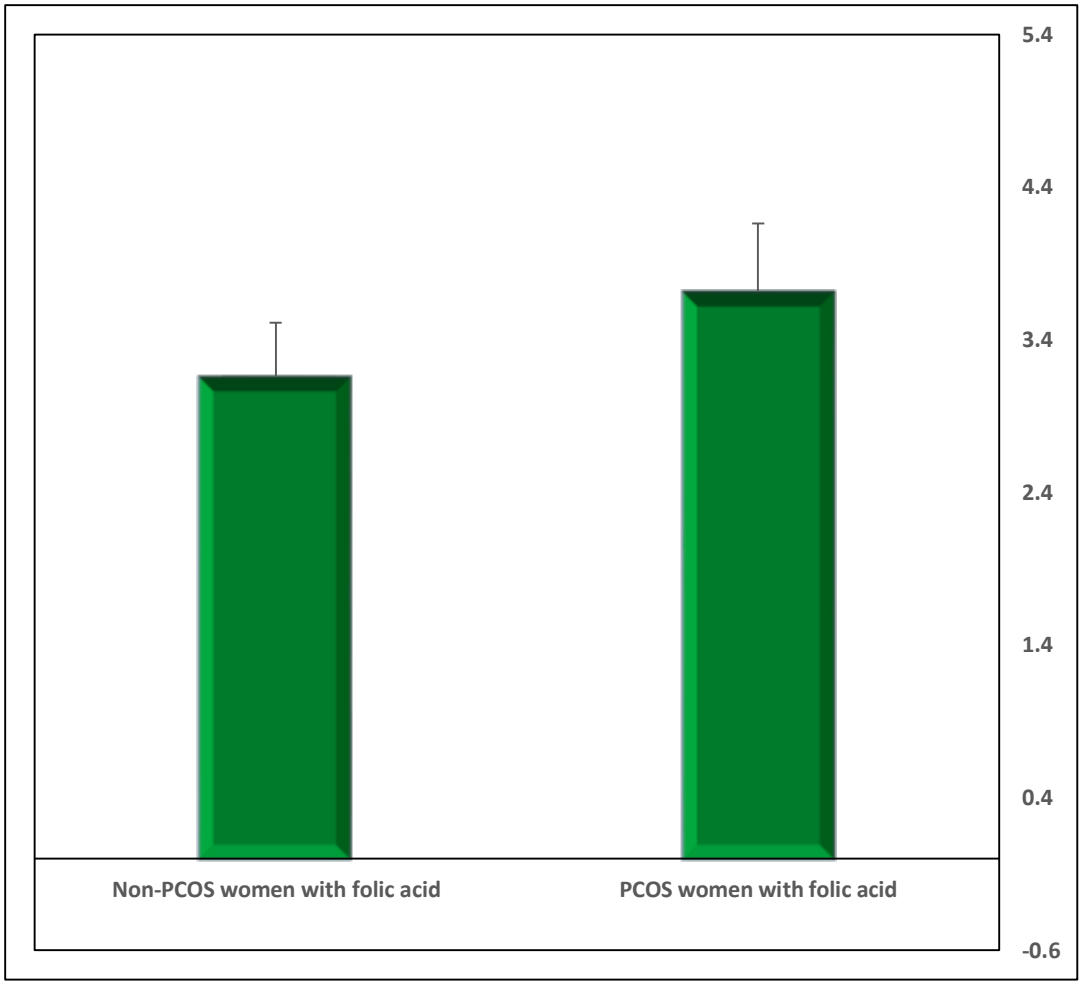

Figure 1: Expression of MDA level in PCOS and non-PCOS women following folic acid supplementation, 5mg / day for 3 months. Data is expressed as the mean change in MDA level (± SEM) (n =40 in each group). Statistical significance was determined by one-way ANOVA testing followed by Dunnett correction for multiple comparisons.

2- Effect of folic acid intake on MDA level in PCOS women with folic acid (group 1) and PCOS women without folic acid (group 3) women.

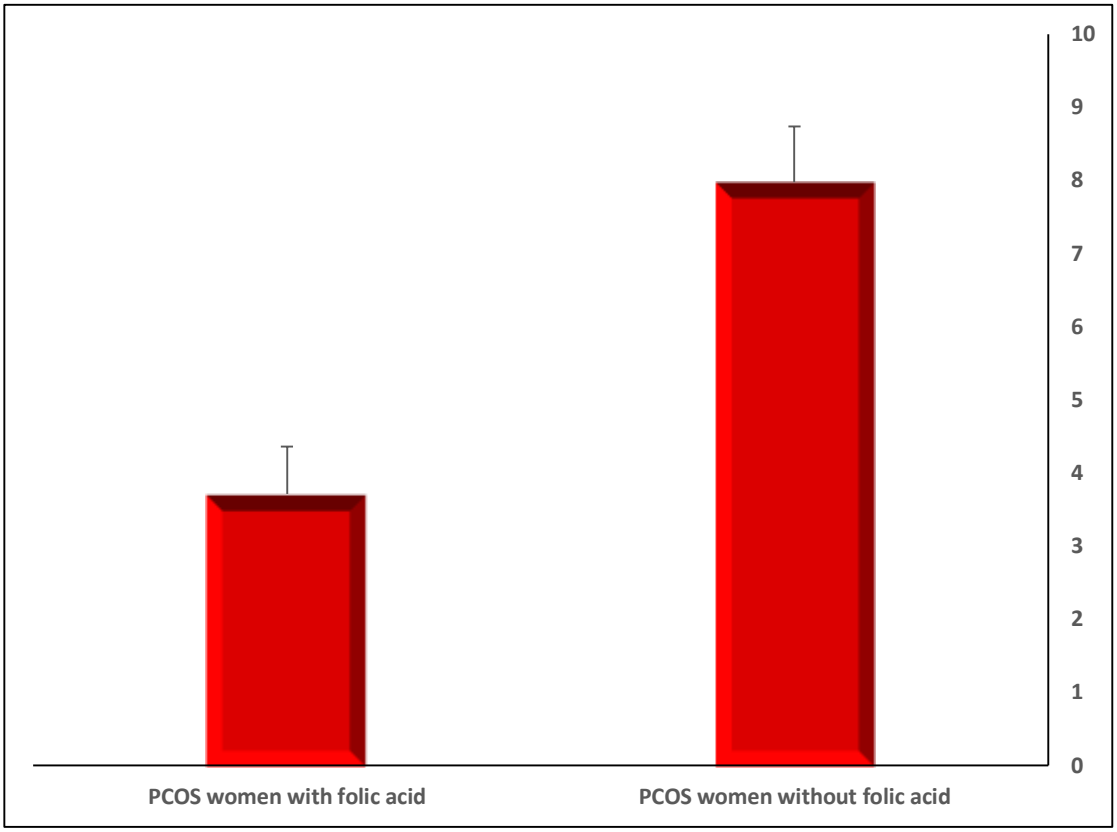

Figure 2: Expression of MDA level in PCOS women following with and without folic acid supplementation, 5mg / day for 3 months. Data is expressed as the mean change in MDA level (± SEM) (n =40 in each group). Statistical significance was determined by one-way ANOVA testing followed by Dunnett correction for multiple comparisons.

3- Comparison between non-PCOS women with folic acid (group 1) and PCOS women without folic acid (group 3).

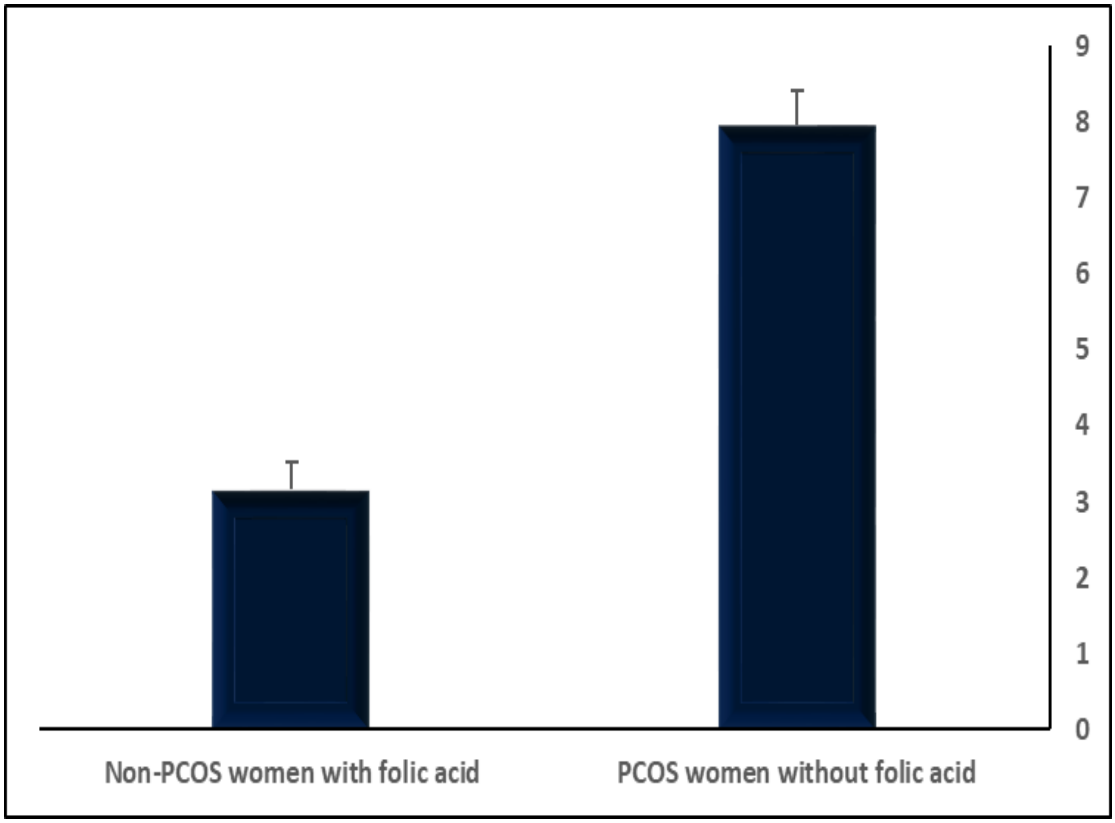

Figure 3: Expression of MDA level in non PCOS women with folic acid 5mg/day for 3 months and PCOS WOMEN without folic acid supplementation. Data is expressed as the mean change in MDA level (± SEM) (n =40 in each group). Statistical significance was determined by one-way ANOVA testing followed by Dunnett correction for multiple comparisons.

IV. Discussion

As previously discussed, oxidative stress is defined as the imbalance between the production of reactive oxygen species and the capacity of cellular antioxidant systems to effectively remove these potentially cytotoxic chemicals [26]. Oxidative stress has now been linked with several neurological and non-neurological disorders [27,28], and therefore it is important to determine if therapeutic agents used in treating these disorders influence a cells response to oxidative stress.

PCOS has been regarded as a chronic systemic disease instead of the simple local disease, and it is frequently associated with insulin resistance (IR), hyperandrogenemia, chronic inflammation, and oxidative stress (OS), though the pathogenesis mechanism has not been well defined [29–30].

Lipid peroxidation mediated by free radicals is considered to be the major mechanism of cell

membrane destruction and cell damage. Free radicals are formed in both physiological and pathological conditions in mammalian tissues [31]. The uncontrolled production of free radicals is considered as an important factor in the tissue damage induced by several pathophysiologies [32]. Alteration in the oxidant -antioxidant profile is known to occur in polycystic ovary syndrome [33].

In the present study, our data revealed that folic acid supplementation, 5mg/day for 3 months was found to decrease the MDA level in PCOS significantly ($p<0.05$) in comparison to PCOS women without folic acid intake (figure 2). In addition, MDA level was significantly increased in PCOS women without folic acid supplementation ($p<0.05$) as compared to non-PCOS women with folic acid (figure 1). Furthermore, there was no significant changes between PCOS women and non PCOS women on folic acid intake (figure 3).

These results are in consistent with Kuscu *et al.* who compared blood MDA level in PCOS patients with healthy controls. They showed the MDA level was significantly higher in the PCOS group but was independent of obesity. [34]. In another study, Zhang *et al.* demonstrated that serum MDA levels in PCOS patients were significantly higher than the control group, but BMI and age were not recorded. [35].

Moreover, Palacio *et al.* compared PCOS patients with BMI and age matched controls. They demonstrated that higher levels of erythrocyte MDA were seen in PCOS patients compared with controls. These results also were found by Sabuncu *et al* [36,37]. Fenkci *et al.* investigated TAC level in PCOS patients compared with the age, BMI, and smoking status matched controls. They demonstrated that the TAC level was significantly lower in PCOS patients [38].

In addition to that, MDA level in PCOS reported in several studies. One meta-analysis showed that circulating mean MDA concentrations according to the age and BMI were increased 47% in women with PCOS compared with controls [39].

The data from this study tend to be in agreement with those of a previous study in Saudi Arabia, which showed lower TAC levels among PCOS women compared to non-PCOS women [40]. Hilali et al similarly reported decreased TAC levels among PCOS women compared to the control group [41].

V. Conclusion

The study provides supportive evidence that oxidative stress might play a role in the pathogenesis of PCOS, and hence, these parameters may be suggested as diagnostic markers for early diagnosis and screening of high-risk groups. In addition, from this study, it is found that folic acid might play an important role in reducing the oxidative insult which might play a crucial role in PCOS.

VI. Recommendation

Although frequent research has been conducted on oxidative stress and PCOS, the exact mechanism behind that is still unknown. Further studies were needed with more oxidative stress

parameters, increased sample size, and in combination with the hormonal changes, insulin resistance status evaluation.

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