Original Article

Role of Chromium Versus Metformin Supplementations as Adjuvant for Ovulation Induction By Clomiphene Citrate in Infertile Patients With Polycystic Ovary Syndrome : Randomized Controlled Trial

Tamer Farouk Borg, Asmaa Gaballah Sayed Hasan, Mohamed S. Khallaf, Hossam Mohamed Mohamed Hemeda, Marwan Osama Elkady

Department of Obstetrics and Gynecology, Faculty of Medicine, Ain-Shams University, Cairo, Egypt

ABSTRACT

Aim: This study aimed to explore the effect of chromium picolinate compared to Metformin supplementation with ovulation induction in polycystic ovary syndrome, In particular, its effect on insulin sensitivity, ovarian response and pregnancy rate.

Materials and Methods: This study was conducted as a prospective study, aimed to compare the effect of Chromium and Metformin supplementations on ovulation rate in Polycystic ovary patients undergoing ovulation induction. The present study included 140 women divided into 2 groups each is 70 infertile women diagnosed as polycystic ovary syndrome according to Rotterdam criteria 2017: (oligo-ovulation or anovulation, clinical or biochemical signs of hyperandrogenism, polycystic ovaries on ultrasound).

Results: Fasting blood sugar (FBS) and fasting insulin level were significantly decreased in metformin group than in Chromium picolinate group after 3 months of treatment (*p=0.006*) (*p=0.026*) respectively. Testosterone significantly decreased in both groups at follow up as compared to basal level (*P-value <0.001, <0.001* respectively with no significant difference between the studied groups regarding testosterone reduction (*P-value=0.416*) after 3 months of treatment. The two study groups were not significantly different regarding ovulation and pregnancy rates(*P-value 0.157, 0.550*) respectively after 3 months of treatment. The patients who received metformin experienced more side effects compared to those receiving chromium picolinate (*p=0.001*).

Conclusion: In view of the aforementioned findings, we recommend that metformin could be replaced by chromium picolinate in some PCOS patients, as its better tolerated than metformin due to lower side effects and no significant differences were observed between the two groups regarding ovulation and pregnancy rates.

Key Words: Chromium picolinate, Clomiphen citrate, Metformin, Polycystic ovary Syndrome (PCOS)

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Corresponding Author: Asmaa Gaballah Sayed Hasan, Department of Obstetrics and Gynecology, Ain-Shams University, Cairo, Egypt, **Tel.:** 01022769106, **E-mail:** sasmaagaballah@med.asu.edu.eg

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common reproductive endocrine diseases that impact many young women worldwide. This hormonal problem affects 4-18% of women of reproductive age exhibiting various symptoms, such as irregular menstruation, hirsutism, infertility and metabolic disorders[1].

Anovulation and androgen excess have been considered the hallmark diagnostic criteria of the syndrome. Insulin resistance (IR) has been identified as a significant contributor to the pathogenesis of PCOS[2].

Nearly 20% of obese women with PCOS have an impaired Glucose Tolerance Test (GTT) or diabetes. Insulin sensitivity is impaired in PCOS and this finding holds in both the presence and absence of obesity. Evidence from in vivo and in vitro studies suggests that insulin has both direct and indirect effects on androgen levels. Moreover, ovaries removed from the women with PCOS exhibited enhanced androstenedione and testosterone release in response to insulin stimulation. Furthermore, it has been shown that acute increment in insulin levels in the women with PCOS induces rises in androgen levels[3].

Metformin is an FDA-approved biguanide for the management of type 2 diabetes mellitus (T2DM). Although its mechanism of action remains obscure, metformin was shown to activate adenosine monophosphate-activated protein kinase (AMPK) pathway, inhibiting hepatic production of glucose, reducing oxidation of fatty acids,

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and increasing peripheral tissue uptake of glucose. Metformin is believed to lower fasting serum insulin levels in insulin-resistant states without inducing hypoglycemia, and helps reduce insulin requirements in insulin-dependent and non-insulin-dependent diabetes[4].

Interest in the use of metformin, an insulin-lowering drug, in PCOS increased when it was appreciated that insulin resistance played an important role in the pathophysiology of the disorder. Metformin is typically the first-line treatment for patients with type 2 diabetes; it is not approved for use in prediabetes or PCOS, although it is often prescribed for treatment of these conditions. Early trials in women with PCOS subsequently demonstrated a small benefit for weight reduction, a decrease in serum androgens (without improvement in hirsutism), and restoration of menstrual cycles in approximately 50 percent of women with oligomenorrhea (although not always ovulatory). Early data also suggested that metformin was effective for ovulation induction in anovulatory women with PCOS. As a result, metformin was used "off-label" for a number of these indications. Although there was widespread enthusiasm for metformin therapy in women with PCOS for a number of years, clinical data do not support the use of metformin for treatment of hirsutism or as first-line treatment for ovulation induction in this population. However, whether metformin has a beneficial long-term effect upon reducing the risk of conversion to diabetes from prediabetes has not been addressed[5].

The micronutrient chromium, which is gaining popularity as a dietary supplement to improve the actions of insulin under insulin-resistant conditions, merits attention. The potential role of chromium in regulating blood sugar was first indicated in the late 1950s. The ‘essentiality’ of chromium in human nutrition was suggested when it was found that chromium supplementation reversed glucose intolerance in hospitalized patients receiving long-term total parenteral nutrition[6].

Chromium potentiates the biological action of insulin. A number of studies have found that cr. supplementation can improve insulin sensitivity and blood sugar control in animals and humans with insulin resistance, elevated blood sugar, impaired glucose tolerance and diabetes. Chromium picolinate supplementation significantly lowered fasting insulin and glucose levels[7].

It improves insulin sensitivity at the insulin receptor level, which should theoretically help with the IR and the obesity seen in PCOS. Chromium supplements have become, for instance, the second most commonly taken nutritional supplement in the USA[8].

In women with polycystic ovary syndrome, chromium picolinate (200 µg/d) improves glucose tolerance compared with placebo but does not improve ovulatory frequency or hormonal parameters[9].

While other studies show that chromium picolinate improved insulin resistance, fasting insulin level, bodyweight; and induced ovulation and regular menstrual cycles in PCOS patients[9].

AIM OF THE STUDY

The aim of this study is to compare the effect of Chromium and Metformin supplementations on ovulation rate in Polycystic ovary patients undergoing ovulation induction.

PATIENTS AND METHODS

Study population: This study was conducted as a prospective study, aimed to compare the effect of Chromium and Metformin supplementations on ovulation rate in Polycystic ovary patients undergoing ovulation induction.

The present study included 140 women divided into 2 groups each is 70 infertile women diagnosed as polycystic ovary syndrome according to Rotterdam criteria 2017: (oligo-ovulation or anovulation, clinical or biochemical signs of hyperandrogenism, polycystic ovaries on ultrasound).

Inclusion criteria: Patient with primary or secondary infertility diagnosed as polycystic ovary syndrome according to Rotterdam criteria. Women aging (17 -35 years old).

Exclusion criteria: Male factor. Uterine and cervical causes of infertility. Hypothalamic pituitary overian disorders. .Tubal causes of infertility. Any endocrinal abnormalities which might affect the hormonal level as DM, adrenal disorders. Extremes of weight (BMI < 19 or >35).

Patients were divided into two groups: The first group (n)=70 patients who were given chromium supplementation in a dose of 1000 microgram chromium piclonate (Chromitron Capsule Manufactured by (Nerhadou International for Pharmaceuticals and Nutraceuticals) daily for three months with clomiphene citrtea of 100 mg (2 Clomid Tablets Manufactured by Global NAPI Pharmaceuticals) daily for 5 days from the third to the seventh day of each cycle for three successive ovarian cycles. The second group (n)=70 patients who were given metformin supplementations 500 mg) 3 times daily (cidophage 500mg tablets Manufactured by Chemical Industries Development (CID)) with clomiphene citrate of 100 mg (2 Clomid Tablets Manufactured by Global

NAPI Pharmaceuticals) daily for 5 days from the third to the seventh day of each cycle for three successive ovarian cycles (Figure 1).

Interventions: Women attended to the outpatient clinic and were subjected to history taking, age, cycle regularity, infertility, hirsutism, acne, overweight or obesity, hypertension, diabetes mellitus, family history of PCOS and scalp hair loss.

Clinical examination: Clinical examination was done including general examination including general appearance, BMI and signs of hyperandrogenism e.g., hirsutim and acne. Abdominal examination to exclude any organic clinically detectable pathologic lesions and hair distribution. Pelvic examination: included inspection of the external genitalia, speculum examination of the vagina, cervix and bimanual assessment of uterine size and position as well as exclusion of adnexal masses.

Laboratory investigations : Revision of patients Laboratory investigations to fulfill the criteria: routine investigations including CBC, fasting and postprandial blood sugar, urine analysis, HbA1c will be done. Endocrinological evaluation including: measuring thyroid-stimulating hormone, free thyroxin (T4), and FSH, LH, E2 levels on the 3rd day of the menstrual cycle, semen analysis, free testosterone, serum prolactin and progesterone on the 21st day of the cycle. Sonography: performed using Samsung H60 with convex probe (multi-frequency AD 2~ 8 MHz) to perform trans-vaginal examination. Examination will be performed on the 2nd or 3rd day of the cycle.

Ultrasound criteria for polycystic ovary syndrome: (Enlarged ovaries with thickened sclerotic capsules and an abnormally high number of follicles are present. The follicles may concurrently exist in varying states of growth, maturation, or atresia. One or both ovaries demonstrate 12 or more follicles measuring 2-9 mm in diameter, or the ovarian volume exceeds 10 cm^3).

The two groups were compared before treatment and at the end of the treatment as regard the following criteria: primary outcome including ovulation rate after the first and third month of treatment. (Ovulation will be documented U/S and midluteal progesterone.) Each woman will be subjected to ovarian stimulation for a maximum of 3 consecutive cycles except if she gets pregnant in the first or second cycle. guided by Transvaginal sonography (TVS) scan, which will be performed for monitoring of follicular growth (folliculometry); starting from day 9 of the stimulation cycle and repeated every 48 hours. When there will be at least one follicle ≥ 18 mm in diameter, final oocyte maturation will be induced by intramuscular administration of 5000 IU of HCG and timed intercourse will be advised. If spontaneous ovulation hasn't occured[10].

Secondary outcome included pregnancy rate (clinical pregnancy rate after the first , second and third month of treatment documented by fetal cadiac activity on ultrasono-graphic examination.). Change in Fasting blood sugar, change in fasting insulin level, change in BMI and change in free testesterone.

Clinical side effects of drugs used chromium (watery diarrhea, vertigo, headache, abdominal discomfort, urticaria) Metformin (nausea, vomiting, diarrhea, loss of appetite, taste disturbance, urticaria). Colmiphene citrate (vasomotor flushes, pelvic discomfort, breast discomfort, headache, visual symptoms, dermatitis, spotting amenorrhea).

RESULTS

One hundred and forty women were divided into 2 groups each is 70 infertile women diagnosed as polycystic ovary syndrome according to Rotterdam criteria 2017, were enrolled into the present study. Demographic characteristics among the studied groups are presented in Table 1.

BMI significantly decreased in both groups as compared to basal level at month-3 (*P-value<0.001*, *<0.001* respectively), non-significantly higher in Metformin group than in Chromium group (*P-value=0.062*) (Table 2). Fasting blood glucose significantly decreased in both groups at follow up as compared to basal level (*P-value<0.001, <0.001* respectively) and was significantly lower in Metformin group than in Chromium group (*P-value=0.006*) (Table 6). Fasting insulin significantly decreased in both groups at follow up as compared to basal level (*P-value<0.001, <0.001* respectively) and was significantly lower in Metformin group than in Chromium group (*P-value=0.026*) (Table 7). Testosterone significantly decreased in both groups at follow up as compared to basal level (*P-value<0.001,<0.001* respectively) with No significant difference between the two groups (Table 8). Ovulation was non-significantly more frequent in Metformin group than in Chromium group at months 1 and 3 (*P-value=0.262* and *0.157* respectively) (Table 4). Pregnancy was non-significantly more frequent in Metformin group than in Chromium group in months 1, 2 and 3 (*p-value=0.999, 0.459* and *0.550* respectively) (Table 5). Overall, the patients who received metformin experienced more side effects compared to those receiving chromium picolinate (Table 9).

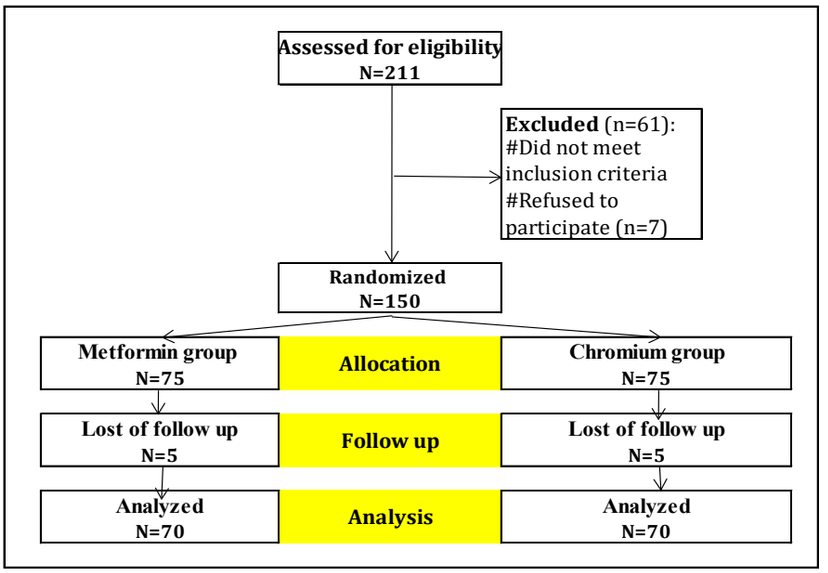

Fig. 1: Flow chat of the studied cases

Table 1: Demographic characteristics among the studied groups

Items	Measure	Metformin (N=70)	Chromium (N=70)	*P-value*
Age (years)	Mean±SD	28.0±4.1	28.1±4.1	^ 0.935
	Range	20.0–35.0	20.0–35.0	
Parity	Multi	26 (37.1%)	22 (31.4%)	# 0.476
	Nulli	44 (62.9%)	48 (68.6%)	
Duration (years)	Mean±SD	2.7±1.1	2.9±1.1	^ 0.301
	Range	1.0–5.0	1.0–5.0	

IQ: Interquartiles. ^Independent t-test. #Chi square test

Table 2: BMI (kg/m2) among the studied groups

Time	Measure	Metformin (N=70)	Chromium (N=70)	^*P-value* (groups)
Pre treatment	Mean±SD	26.4±4.0	26.6±3.4	0.770
	Range	19.1–32.6	19.6–33.1	
	N	52	55	
Month-3	Mean±SD	24.5±3.8	23.9±3.5	0.406
	Range	16.8–30.4	16.8–30.7	
Change (month 3 -pre)	Mean±SD	-2.6±0.3	-2.4±0.3	0.062
	Range	-3.5–-2.1	-3.0–-1.5	
#*P-value* (month 3)		<0.001*	<0.001*	
		Value of Metformin relative to Chromium		
Items		Mean±SE	95% CI	
Change (month-3)		-0.2±0.1	-0.4–0.0	

^Independent t-test #Paired t-test. CI: Confidence interval, *Significant

Table 3: Serum progesterone (ng/ml) among the studied groups

Time	Measure	Metformin (N=70)	Chromium (N=70)	^*P-value* (groups)
Pre treatment	Mean±SD	6.9±1.9	6.6±1.8	0.485
	Range	2.3–9.5	2.3–9.4	
Month-1	Mean±SD	10.0±2.1	9.4±2.0	0.083
	Range	6.4–15.8	5.4–14.0	
Change (month 1 -before)	Mean±SD	3.2±1.8	2.8±1.0	0.123
	Range	1.6–9.4	1.2–7.5	
#P-value (month 1)		<0.001*	<0.001*	
	N	59	62	
Month-3	Mean±SD	15.1±5.2	13.2±5.3	0.054
	Range	5.9–27.3	4.9–27.3	
Change (month 3 -pre)	Mean±SD	8.3±5.2	6.6±4.5	0.063
	Range	0.3–21.0	0.5–19.3	
#*P-value* (month 3)		<0.001*	<0.001*	
		Value of Metformin relative to Chromium		
Items		Mean±SE	95% CI	
Change (month-1)		0.4±0.2	-0.1–0.9	
Change (month-3)		1.6±0.9	-0.1–3.4	

^Independent t-test #Paired t-test. CI: Confidence interval, *Significant

Table 4: Ovulation among the studied groups

Time	Metformin (N=70)	Chromium (N=70)	*P-value*	Relative rate (95% CI)
Month-1	23 (32.9%)	17 (24.3%)	#0.262	1.35 (0.80–2.30)
N	59	62		
Month-3	45 (76.3%)	40 (64.5%)	#0.157	1.18 (0.94–1.49)

#Chi square test. §Fisher's Exact test. *Significant, CI: Confidence interval

Table 5: Cummulative pregnancy among the studied groups

Time	Metformin (N=70)	Chromium (N=70)	*P-value*	Relative rate (95% CI)
Month-1	2 (2.9%)	1 (1.4%)	§0.999	2.00 (0.19–21.60)
Month-2	11 (15.7%)	8 (11.4%)	#0.459	1.38 (0.59–3.21)
Month-3	18 (25.7%)	15 (21.4%)	#0.550	1.20 (0.67–2.19)

#Chi square test. §Fisher's Exact test. *Significant. CI: Confidence interval

Table 6: Fasting blood glucose (mg\dl) among the studied groups

Time	Measure	Metformin (N=70)	Chromium (N=70)	^*P-value* (groups)
Pre treatment	Mean±SD	97.7±12.6	98.4±14.0	0.756
	Range	75.0–121.0	73.0–128.0	
	N	52	55	
Month−3	Mean±SD	83.8±9.9	90.2±13.0	0.006*
	Range	70.0–110.0	70.0–119.0	
Change (month 3 -pre)	Mean±SD	-13.6±7.9	-7.9±5.8	<0.001*
	Range	-36.0–-4.0	-20.0–5.0	
#*P-value* (month 3)		<0.001*	<0.001*	
Value of Metformin relative to Chromium				
Items		Mean±SE	95% CI	
Glucose change (month−3)		-5.7±1.3	-8.3–-3.1	

^Independent t-test #Paired t-test. CI: Confidence interval, *Significant

Table 7: Fasting insulin level (mlU\L) among the studied groups

Time	Measure	Metformin (N=70)	Chromium (N=70)	^*P-value* (groups)
Pre treatment	Mean±SD	15.6±4.3	15.3±3.8	0.668
	Range	3.5–22.6	3.3–22.2	
	N	52	55	
Month-3	Mean±SD	11.8±3.3	13.4±3.8	0.026*
	Range	1.9–19.2	2.9–19.6	
Change (month 3 -pre)	Mean±SD	-3.5±2.6	-1.9±3.6	0.010*
	Range	-10.3–3.0	-9.0–5.9	
#*P-value* (month 3)		<0.001*	<0.001*	
Value of Metformin relative to Chromium				
Items		Mean±SE	95% CI	
Insulin change		-1.6±0.6	-2.8–-0.4	

^Independent t-test #Paired t-test. CI: Confidence interval, *Significant

Table 8: Serum testesterone (pg\ml) among the studied groups

Time	Measure	Metformin (N=70)	Chromium (N=70)	^*P-value* (groups)
Pre treatment	Mean±SD	2.0±1.3	1.9±1.0	0.412
	Range	0.2–5.7	0.8–6.1	
	N	52	55	
Month-3	Mean±SD	1.5±0.6	1.5±0.8	0.839
	Range	0.4–3.2	0.2–3.2	
Change (month 3 -pre)	Mean±SD	-0.6±1.0	-0.4±0.5	0.416
	Range	-3.2–1.2	-3.2–0.2	
#*P-value* (month 3)		<0.001*	<0.001*	
Value of Metformin relative to Chromium				
Items		Mean±SE	95% CI	
Testestrone change		-0.1±0.2	-0.4–0.2	

^Independent t-test #Paired t-test. CI: Confidence interval, *Significant

Table 9: Side effects among the studied groups

Side effects	Metformin (N=70)	Chromium (N=70)	*P-value*	Relative rate (95% CI)
Loss of appitite	3 (4.3%)	12 (17.1%)	#0.014*	0.25 (0.07–0.85)
Abdominal discomfort	13 (18.6%)	4 (5.7%)	#0.020*	3.25 (1.11–9.48)
Watery diharrea	5 (7.1%)	0 (0.0%)	§0.059	--
Vertigo	8 (11.4%)	3 (4.3%)	#0.116	2.67 (0.74–9.64)
Headache	2 (2.9%)	7 (10.0%)	§0.165	0.29 (0.06–1.33)
Urticaria	3 (4.3%)	2 (2.9%)	§1.000	1.50 (0.26–8.70)
Nausea	14 (20.0%)	3 (4.3%)	#0.004*	4.67 (1.40–15.53)
Vomiting	11 (15.7%)	2 (2.9%)	#0.009*	5.50 (1.27–23.92)
Taste disturbance	1 (1.4%)	4 (5.7%)	§0.366	0.25 (0.03–2.18)

#Chi square test. §Fisher's Exact test.*Significant, CI: Confidence interval

DISCUSSION

Polycystic ovary syndrome (PCOS) is the commonest endo-crinopathy amongst young women, with approximately one in five women having ovaries with a polycystic appearance on ultrasound and almost half of those with polycystic ovaries fulfilling the diagnostic criteria for PCOS[11].

Polycystic ovary syndrome (PCOS) is the usual cause of anovulatory infertility. Induction of ovulation with clomiphene citrate (CC) was reported in the 1960s with ovulation rate of 75-80% and a cumulative pregnancy rate of 70-75% after 6-9 cycles of treatment[12].

Chromium is an essential mineral that has an essential role in carbohydrate and lipid metabolism. Chromium has been widely studied in the treatment of hyperglycemia, especially type 2 diabetes, because chromium deficiency leads to disorders in glucose homeostasis and Insulin Resistance (IR)[13].

Although there is no direct evidence of chromium deficiencies in humans, dietary supplements exist to provide supra physiological doses of absorbable chromium3+. Chromium3+ may act clinically by interfering with iron absorption, decreasing the high iron stores that are linked to diabetes and heart disease[14].

Chromium functions as a part of an auto amplification system for insulin signaling and promotes enhancement of insulin sensitivity[15].

The use of metformin in the treatment of PCOS was started in 1998 by Nestler and colleagues with some skepticism Nestler *et al.*[16] but it`s now accepted to be a valuable and inexpensive therapeutic modality[17]. Tang and colleagues have indicated that metformin is highly effective in inducing ovulation and increasing pregnancy rate[18].

Hyperinsulinemia is believed to stimulate ovarian androgen production by direct action on the theca cells and by potentiating LH effects. The local build-up in follicular androgenic signal has been shown to promote premature follicular atresia, primary and pre-antral follicle arrest, and impaired follicle dominance, leading to anovulation. High insulin state further potentiates adrenal androgen secretion by enhancing adrenal response to ACTH[19].

An interest in the role of insulin-sensitizing drugs (ISDs) as a means of reducing compensatory hyperinsulinemia in the hope of improving metabolic and reproductive functions in women with PCOS has grown measurably over the past decade[4].

As data regarding the use of chromium picolinate are not well established so this current research was done in order to compare the effect of metformin and chromium picolinate on ovulation induction and pregnancy rate in patients with PCOS.

This study is a double-blinded prospective randomized clinical trial included 140 infertile women with polycystic ovary syndrome according to Rotterdam criteria 2017: (oligo-ovulation or anovulation, clinical or biochemical signs of hyper-androgenism, polycystic ovaries on ultrasound) were divided into two groups, chromium group (n)=70 patients received chromium supplementation in a dose (1000) microgram chromium piclonate daily for three months with clomiphene citrtea of 100 mg daily for 5 days from the third to the seventh day of each cycle for three successive ovarian cycles. The second group is metformin group (n)=70 patients received metformin supplementations 1500 mg) daily with clomiphene citrate of 100 mg daily for 5 days from the third to the seventh day of each cycle for three successive ovarian cycles, to study and compare the effect of Chromium and Metformin supplementations with ovulation induction in infertile patients with polycystic ovary syndrome on ovulation rate.

In our study, mean age was 28.0±4.1 in metformin group and 28.1±4.1 in chromium group due to the random distribution of the patients into the 2 groups in this work, so there was no significant difference between both group regarding to age.

Also, our study showed statistically significant decrease in both groups ragarding to BMI as compared to basal level at month-3, with no significat difference between the studied groups pretreatment and month-3, which came in agreement with study by Amooee *et al*.[15] found that a significant decrease in BMI in the group receiving metformin (*p=0.041*). Other study by Kishk *et al*.[20] observed a significant decrease in BMI in metformin group and in chromium group and the study by Kazerooni and Dehghan-Kooshkghazi[21], 500 mg metformin was used three times a day and the decrease in BMI was completely overt.

Also, Aruna *et al*.[22] conducted study using 500 mg metformin two times a day in 50 patients and reported a decrease in BMI, and study by Ashoush *et al*.[9] showed a significant reduction BMI (*P < 0.001*) after 6 months from chromium treatment.

On contrary the study by Genazzani *et al*.[23] observed no decrease in BMI in PCOS patients used 500 mg metformin two times a day for 6 month, and study by Lydic *et al*.[24] showed 1000 microgm chromium was used daily in PCOS patients for 2 month with no significant changes in BMI, also, Anderson[25] no changes in BMI after receiving chromium.

The current study showed no significant difference between the studied groups regarding basal month-1 and month-3 progesterone (*P-value=0.485*, *0.083* and *0.054,* respectively). Progesterone as compared to basal level significantly increased in both groups at month-1 (*P-value 0.001, <0.001,* respectively) and at month-3 (*P-value<0.001, <0.001,* respectively). Progesterone elevation was non-significantly higher in Metformin group than in Chromium group at months 1 and 3 (*P-value=0.123* and *0.063,* respectively).

Ovulation assessed by ultrasound and mid-luteal progesterone level over 10 ng/mL Haymond *et al*.[26], occurred in 54 (77.1%) patients in metformin group and 46 (65.7%) patients in chromium group. Ovulation rate was non-significantly more frequent in Metformin group than in Chromium group (*P-value=0.134*), These results supported by Kishk *et al*.[20] study (a study conducted on 60 patients with PCOS, the first group received metformin 500mg twice daily while the other group received chromium picolinate 200µg once daily for 3 months ovulation occurred in 11 (40.7%) patients in metformin group and 12 (44.4%) patients in chromium group.

Also, in the study done by Amooee *et al*.[15] among those who received chromium picolinate, 22(47.8%) patients ovulated during the study period and 9 (19.6%) patients conceived and 20 (43.5%) patients of the metformin group ovulated and 10 (21.7%) conceived during the study period *P value 0.417* and *0.5*, respectively.

In Ashoush *et al*.[9] study conducted on 85 female PCOS patients (20-35 years old) receiving 1000 µg CrP/ day for 6 months), ovulation was seen more often in the study group (1000 µg CrP/ day) over control group (placebo) after 5 months (n = 20, 45.5% vs n = 8, 19.5%; *P = 0.011*) and after 6 months (n = 26, 59.1% vs n = 8, 19.5%; *P<0.001*) respectively, after starting treatment CrP treatment significantly increased the rate of ovulation by almost two folds after 5 months (RR, 2.33; 95% CI: 1.16–4.69) and another three folds after 6 months (RR, 3.03; 95%CI: 1.55–5.91).

In our study, pregnancy rate was non-significantly more frequent in Metformin group 18 (25.7%) than in Chromium group 15 (21.4%) with no significant difference (*p=0.550*). These results supported by Kishk *et al*.[20] pregnancy occurred in 6 (22.2%) patients in group I and 5 (18.5%) patients in group II with no significant difference (*p=0.73*).

So, metformin has nearly the same effect as chromium on the pregnancy rate, and no significant difference between two groups regarding to the ovulation. They concluded that metformin had the same effect as chromium on the ovulation and the pregnancy rate.

The present study showed no significant difference between the studied groups regarding basal fasting glucose (*P-value=0.765*), basal fasting insulin (*P-value=0.668*) and basal testosterone (*P-value=0.412*).

Metformin and chromium groups both showed significant reduction in fasting glucose level (*P-value<0.001, <0.001* respectively), fasting insulin (*P-value<0.001, <0.001* respectively) and testosterone (*P-value<0.001, <0.001* respectively) at follow up as compared to basal level.

Post treatment fasting blood glucose and fasting serum insulin were significantly lower in Metformin group than in Chromium group (*P-value=0.001*) and (*P-value=0.010*) respectively.

These results are supported by those reported by Kishk *et al*.[20] showed significant differences in the values of free testosterone, fasting blood sugar and fasting insulin before and after treatment with metformin and chromium group *P value 0.01, 0.001, 0.001*, respectively and Ashoush *et al*.[9] study showed a significant reduction in FSI (*P = 0.007*) and fasting glucose insulin ratio (*P value 0.047*) as well.

Hummel *et al*.[27] have confirmed the effectiveness of chromium in decreasing FBS and 2 hour glucose, HbA1C, fasting and 2 hour insulin and insulin sensitivity in the patients receiving oral chromium picolinate (1000 µg /d) after two and four months of treatment.

On the contrary, Ashoush *et al*.[9] study showed non- significant changes in FBS in the control or study groups (*P = 0.594* and *0.32* respectively) may due to diet control and restriction of simple sugars, saturated fats and limited total caloric intake and physical exercise,serum-free testosterone statistically unchanged after 6 months of chromium treatment (*P = 0.42*) as well and Masharani *et al*.[28] study concluded that CrP therapy does not improve insulin sensitivity in normal non-diabetic subjects (*p=0.83*), In a study conducted on 31 non-obese, normoglycemic patients, receiving chromium picolinate 500 µg twice a day. Most probably due to the absence of any IR in the study population.

Also, a study by Aruna *et al*.[22] included 50 Indian women- 25 unmarried women and 25 married, infertile women with PCOS in the age of 15–35 years, receiving 500-mg metformin tablets twice daily for 6 months), found no decrease in FBS and fasting insulin (*P value 0.66, 0.39*) respectively.

Testesterone significantly decreased in both groups at follow up as compared to basal level (*P-value<0.001*, *<0.001,* respectively). Follow up testesterone was non-significantly lower in Metformin group than in Chromium group (*P-value=0.839*).

A study by Amooee *et al*.[15] showed that the serum levels of free testosterone decreased by 0.2 ng/ml and 1.1 ng/ml in chromium and metformin groups, respectivley and the difference was statistically significant (*P value 0.001*). The decreasing effect of metformin on testosterone was reported by Kolodziejczyk *et al*.[29] study included 39 women with PCOS and fasting hyper insulinemia using oral metformin (500 mg three times per day) for 12 weeks and found Metformin therapy resulted in a significant decrease in fasting insulin and total testosterone *P value <0.001, <0.001* respectively, leading to significant improvement of clinical manifestations of hyper-androgenism.

On the contrary, no changes were observed in testosterone level (*P value 0.08*) may due to increase manifestations of hyperandrogenism about (70%) and obesity (39%) in patients before treatment or small sample size, In the chromium group of a study by Lucidi *et al*.[30] no change was found in free levels of testosterone, FBG and fasting insulin (*P value > 0.05*) may due to small chromium dose (200 mcg/d CrP).

Our study showed significant difference according to side effects among both groups regarding Nausea, vomiting and abdominal discomfort which were significantly more frequent in Metformin group than in Chromium group (*P value 0.004, 0.009* and *0.02* respectively), while Loss of appetite was significantly more frequent in Chromium group than in Metformin group (*P value 0.014*). these results were close to Kishk *et al*.[20] who showed no significant differences between chromium picolinate group and metformin group regarding side effects, except for abdominal discomfort which exhibited statistically a significant difference between the two groups (*P= 0.018*). In Albarracin *et al*.[31] chromium had very low side effects. In the study done by Amooee *et al*.[15] the patients who received metformin experienced more side effects compared to those receiving chromium picolinate. Moreover, metformin administration was accompanied by higher incidence of abdominal discomfort (*P=0.002*), nausea (*P=0.028*), vomiting (*P=0.001*), diarrhea (*P=0.001*), and indigestion (*P=0.039*), while chromium picolinate was accompanied by loss of appetite (*P=0.018*) and headache (*P=0.001*).

CONCLUSION

In view of the aforementioned findings, we recommend that metformin could be replaced by chromium picolinate in some PCOS patients, as its better tolerated than metformin due to lower side effects and no significant differences were observed between the two groups regarding ovulation and pregnancy rates.

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