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Comparative Study between Chromitron Versus Metformin as an Adjuvant Agent for Ovulation Induction with Letrozole in Patients with Polycystic Ovary Syndrome

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a prevalent reproductive endocrine condition affecting many young women globally. Metformin being the primary treatment for type two diabetes may affect ovulation.

Objective: To evaluate the impacts of supplementation of chromium picolinate with induction of ovulation in PCOS on those of metformin supplementation, focusing on the effects on the response of the ovary, sensitivity of insulin, & rate of pregnancy.

Materials & Methods: This was a double-blinded and prospective research that was carried out on 120 women who were undergoing ovulation induction and were separated into two groups, each consisting of 60 infertile women who met the Rotterdam criteria for PCOS in 2017. The study was conducted at Damanhour Medical National Institute from August 2023 to January 2024.

Results: There wasn't significant variance among the two groups in terms of demographic characteristics, cumulative pregnancy, & ovulation rate. We started the pretreatment at month-1, made a change from month-1 to month-3, and continued the change from month-1. Fasting insulin during the follow-up was considerably lower in comparison with the baseline level in each group. Compared to the chromium group, the metformin group was noticeably lower.

Conclusion: We advise some PCOS patients to switch from metformin to chromium picolinate because it was less likely to cause side effects, was better tolerated, and did not significantly differ from the other group regarding rates of pregnancy and ovulation.

Keywords: Clomiphene citrate, Chromium picolinate, Polycystic ovary syndrome, Metformin**.**

INTRODUCTION

An enormous number of young women are affected by the reproductive endocrine disorder, PCOS, which is quite common throughout the world. This hormonal issue causes hirsutism, irregular menstruation, infertility, & metabolic problems in four to eighteen percent of fertile women [(1)]. Anovulation and androgen excess are the condition's characteristic diagnostic symptoms. Insulin resistance has been found to be a significant factor in the development of PCOS [(2)].

Approximately twenty percent of obese females with PCOS also have diabetes or a reduced glucose tolerance test (GTT). Insulin sensitivity is reduced in PCOS, & this finding holds true regardless of fat. Research, both in vitro and in vivo, has demonstrated that insulin influences androgen levels directly and indirectly. Furthermore, the PCOS-affected women's ovaries were removed, producing more testosterone and androstenedione in response to insulin stimulation. Also, it has been shown that in females with PCOS, an abrupt rise in insulin concentrations results in an increase in concentrations of androgen [(3)].

Biguanide metformin has been permitted by the FDA for the control of type 2 DM. Metformin has been shown to stop the liver from making glucose, activate the AMPK pathway, improve glucose absorption in peripheral tissue, and lower fatty acid oxidation. However, its exact mechanism of action is still unknown. Metformin is believed to help diabetes patients, both insulin-dependent and non-dependent, who need less insulin by reducing blood insulin levels during fasting without producing hypoglycemia [(4)].

Chromium enhances insulin's physiologic impact. Various studies have shown that using chromium supplements can improve the body's response to insulin and regulate blood sugar levels in people and animals suffering from conditions such as high blood sugar, insulin resistance, impaired glucose tolerance, & diabetes. Supplementing with chromium picolinate led to a considerable reduction in fasting insulin & glucose levels [(5)]. Chromium picolinate (200 mg/d) improves glucose tolerance in people with PCOS compared to a sugar pill. Hormonal parameters and the number of ovulation cycles are not affected. Other studies suggest that chromium picolinate aids PCOS patients in managing their menstrual cycles, stimulating ovulation, raising fasting insulin levels, and reducing insulin resistance [(6)].

The goal of this research was to assess the impacts of chromium picolinate supplementation on induction of ovulation in PCOS on those of metformin supplementation, focusing on the effects on the response of the ovary, sensitivity of insulin, and rate of pregnancy.

PATIENTS AND METHODS

This double-blinded prospective research was carried out on 120 women who were undergoing ovulation induction and were separated into two groups. Each group included 60 infertile women who satisfied the Rotterdam criteria 2017 for PCOS, which includes criteria such as oligo-anovulation or ovulation, biochemical or clinical symptoms of hyperandrogenism, & the presence of polycystic ovaries as confirmed by ultrasonography. The initial group consisted of sixty cases who were given a daily dose of one thousand micrograms of chromium picolinate for 3 months, along with a daily dose of one hundred milligrams of clomiphene citrate for five days during the 3rd to 7th day of each ovarian cycle for 3 consecutive cycles. The 2nd group, also consisted of sixty cases who received a daily dose of 1500 milligrams of metformin along with the same dosage of clomiphene citrate & cycle schedule as that of the first group. The research was conducted at Damanhour Medical National Institute between August 2023 and January 2024.

Inclusion criteria: PCOS has been discovered in a patient presenting with either primary or secondary infertility. Women with age ranging from seventeen to thirty-five years.

Exclusion criteria: The male factor, uterine & hypothalamus pituitary ovarian problems, cervical causes of infertility, tubal causes of infertility, and any endocrine abnormalities like adrenal diseases and diabetes mellitus, as well as extreme weight (body mass index below nineteen or above thirty-five kg/m^2), are all factors that may alter the hormone level.

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There were two distinct groups of cases: The initial group of cases (n = 60) were administered a daily dose of one thousand micrograms of chromium picolinate (Capsule of Chromitron, produced by Nerhadou International for Pharmaceuticals & Nutraceuticals) for a duration of 3 months. Additionally, they were given one hundred milligrams of clomiphene citrate (two tablets of Clomid, produced by Global NAPI Pharmaceuticals) per day for five days, specifically from the 3rd to the 7th day of each menstrual cycle, for three consecutive ovarian cycles. The 2nd group of cases (n = 60) received only clomiphene citrate of one hundred milligrams (two tablets of Clomid) per day for five days, following the same schedule as the first group, for 3 successive ovarian cycles. Additionally, they received five hundred milligrams of metformin supplements, to be taken three times a day [Virophage tablets, manufactured by Chemical Industries Development (CID)].

Interventions: Women who visited the outpatient clinic underwent a history-taking process that included questions on cycle regularity, age, hirsutism, infertility, weight gain or obesity, acne, diabetes mellitus, high blood pressure, and a polycystic ovarian syndrome family history.

Clinical examination: We conducted a clinical evaluation that included general assessment (body mass index, appearance, and hyperandrogenism symptoms, such as acne, luteinizing hormone, and hirsutism), examination of the pelvis, and examination of the abdomen.

Laboratory investigations: Regular laboratory tests such as fasting and postprandial blood glucose, CBC, HbA1c, and analysis of urine. Free thyroxin, TSH, follicle-stimulating hormone, and E2 levels were measured throughout the third day of the menstrual cycle. Free testosterone, serum prolactin, semen analysis, & levels of progesterone were measured on the cycle's twenty-first day.

A Samsung H60 with a convex probe (multi-frequency AD 2 8 MHz) was used in transvaginal sonography. The screening day was either the second or third cycle day.
Using ultrasounds to diagnose PCOS. There was an abnormally high number of follicles, thicker sclerotic capsules & larger ovaries. Follicles could be present simultaneously in different stages of development, maturation, or atresia. In one or both ovaries, at least twelve follicles measuring two-to-nine millimeters in diameter are present, or the ovarian volume is greater than ten cubic centimeters.

The following criteria were used to compare the two groups before and after the treatment. We compared the two groups after the first and third months of therapy.

Outcomes: The ovulation rate was the primary outcome. The study provided both midluteal progesterone and ultrasound documentation of ovulation. Except in cases where a woman becomes pregnant during the first or second cycle, each underwent stimulation of the ovaries for up to three cycles in a consecutive cycle. A transvaginal sonography (TVS) scan was done starting the ninth day of the stimulation cycle and then every forty-eight hours after that to measure the size of the follicles (folliculometry). We stimulated the final oocyte maturation through timed sexual activity, and we suggested a five thousand IU intramuscular HCG shot once we found at least one follicle smaller than eighteen millimeters in diameter.
The secondary outcome included the clinical rate of pregnancy following the 1st, 2nd, and 3rd months of treatment, as demonstrated by the action of the fetal heart on ultrasonographic testing, as well as changes in fasting insulin, fasting blood sugar, free testosterone, BMI, and body mass index.

Adverse effects: Clinical adverse effects of chromium-containing medications include urticaria, vertigo, headaches, and watery diarrhea. Metformin can cause symptoms such as vomiting, diarrhea, nausea, vomiting, loss of appetite, altered taste, and urticaria. Clomiphene citrate manifests symptoms such as amenorrhea, dermatitis, headaches, pelvic pain, breast pain, and vasomotor flushes.

Ethical Consideration: The medication utilized in the investigation is confirmed by the Egyptian Ministry of Health. The Ethics Committee of the GOTHI Research Centre approved the research protocol (Ethical approval ID: HD00175). Prior to enrollment, written informed consents were gathered from individuals or their legal representatives. The purpose of this study was to perform research on humans in compliance with the Declaration of Helsinki, the code of ethics of the World Medical Association.

Statistical analysis: The collected data was reviewed & manually coded. The Statistic Package for Social Science Version 22 (SPSS 22) for Windows was employed to conduct statistical analysis on the numerical codes that were inputted into the computer. For parametric variables, range, standard deviation, and mean were required. For non-parametric variables, range, median, & interquartile range and for categorical variables, range, number, and percentage were required. The subsequent assessments were implemented: The Chi square test (X^2) was used for qualitative data comparison, along with independent and paired t-tests, confidence intervals (CI), interquartile range, and Fisher's exact test. The coefficient interval was set at ninety-five percent. The following probability (P) values were used to identify the significance level. Statistical significance was defined as a P-value ≤ 0.05.

RESULTS

There was no significant variance among both groups concerning demographic characteristics (parity, age, & duration), and when compared to the baseline level at month three, BMI significantly fell in both groups (P-values 0.001 and 0.001, correspondingly). Nonetheless non-significantly greater in the group of metformin than in the group of chromium (P-value = 0.062) **(Table 1)**.

Table (1): Demographic data between the groups of research

Items	Measure	Metformin (N=sixty)	Chromium (N=sixty)	P-value
Age (years)	Mean ± SD	28.02 ± 4.4	28.4 ± 4.7	^ 0.648
	Range	21.0–34.0	20.0–37.0	
Parity	Multi	21 (35%)	18 (30%)	# 0.558
	Null	39 (65%)	42 (70%)	
Duration (years)	Mean ± SD	2.5 ± 1.0	2.8 ± 1.2	^ 0.139
	Range	1.0–4.5	1.0–5.4	
Time	**Measure**	**Metformin (N=sixty)**	**Chromium (N=sixty)**	**^P-value (groups)**
Pretreatment	Mean ± SD	25.6±4.1	25.4±3.4	0.771
	Range	18.1–31.2	18.6–32.1	
	N	38	42	
Month-3	Mean ± SD	23.7±3.9	23.2±3.9	0.483
	Range	17.8–31.4	15.8–31.7	
Change (month 3 pre)	Mean ± SD	-2.7±0.5	-2.9±0.6	0.323
	Range	-3.4-1.9	-3.1-1.4	
#P-value (month three)	<0.001*	<0.001*		
Value of Metformin Relative to Chromium				
Items		Mean ± SEM	95% confidence interval	
Change (month three)	-0.19±0.1	-0.3–0.0		

#Paired t-test. ^Independent t-test CI: Confidence interval, *Significant IQ: Interquartile. ^Independent t-test. #Chi square test.

According to progesterone in serum (ng/ml) within the groups under study, there was no statistically significant variance among chromium group & metformin group regarding pretreatment, month-1, change month 1 -before), month-3 and change (month-1) where p-value = 0.09, 0.49, 0.055, 0.13 & 0.062 correspondingly) (Table 2).

Table (2): Serum progesterone (nanograms per milliliter) among the groups of research

Time	Measure	Metformin (N=sixty)	Chromium (N=sixty)	^P-value (groups)
Pretreatment	Mean ± SD	6.9±1.7	6.4±1.6	0.099
	Range	2.3–9.3	2.2–9.3	
Month-1	Mean ± SD	9.8±1.7	9.2±1.7	0.055
	Range	6.3–15.7	5.3–14.1	
Change (month 1 -before)	Mean ± SD	3.2±1.9	2.8±1.2	0.170
	Range	1.59–9.5	1.3–8	
#P-value (month one)		<0.001*	<0.001*	
	N	39	42	
Month-three	Mean ± SD	14.5±4.1	13.1±4.5	0.09
	Range	5.8–26.3	4.8–25.3	
Change (month one)	Mean ± SD	8.4±4.3	7.1±3.7	0.078
	Range	0.29–20.0	0.51–19.4	
#P-value (month 3)		<0.001*	<0.001*	
Value of Metformin Relative to Chromium				
Items		**Mean ± SE**		95% confidence interval
Change (month one)		0.39±0.1	-0.09–0.08	
Change (month three)		1.5±0.8	-0.09–3.3	

At months 1 and 3, the metformin group had a non-significantly higher ovulation rate than the chromium group (P-values, 0.26 & 0.157, correspondingly) (Table 3).

Table (3): Ovulation among the groups of research

Time	Metformin (N=sixty)	Chromium (N=sixty)	P-value	Relative rate (95% confidence interval)
Month one	20 (33.3%)	15 (25%)	#0.315	1.38 (0.82–2.60)
N	46	50		
Month-3	45 (75%)	39 (65%)	#0.231	1.21 (0.96–1.52)

§Fisher's exact test

According to cumulative pregnancy among the studied groups, there was no statistically significant variance among chromium group & metformin group regarding month-1, month-2 and month-3 where (p=0.999), (p=0.45) & (p=0.55) correspondingly (Table 4).

Table (4): Cumulative pregnancy between the groups of research

Time	Metformin (N=sixty)	Chromium (N=sixty)	P-value	Relative rate (95% confidence interval)
Month one	1 (2%)	1 (2%)	#1	2.00(0.23–23.60)
Month two	10 (17%)	10 (17%)	§1	1.33 (0.59–3.19)
Month three	15 (25%)	12 (20%)	#0.51	1.27 (0.70–2.19)

Concentrations of fasting blood glucose were considerably lesser in the metformin group than in the chromium group at follow-up comparing with baseline (P-value=0.001 & 0.001, correspondingly) (Table 5).

Table (5): Fasting blood glucose (milligram per deciliter) between the groups of research

Time	Measure	Metformin(N=sixty)	Chromium(N=sixty)	^P-value (groups)
Pretreatment	Mean ± SD	96.7±11.6	97.4±13.0	0.75
	Range	74.0–120.0	72.0–129.0	
	N	34	42	
Month−3	Mean ± SD	83.2±9.1	91.2±12.8	<0.001*
	Range	71.0–111.0	71.0–120.0	
Change (month three)	Mean ± SD	-13.4±7.5	-7.7±5.4	<0.001*
	Range	-35.0-3.9	-21.0–4.9	
#P-value (month three)		<0.001*	<0.001*	
Value of Metformin Relative to Chromium				
Items		Mean ± SE	95% confidence interval	
Glucose change (month three)		-5.6±1.2	-8.2-3.2	

Fasting insulin during the follow-up considerably lowered in each group related to level of baseline (P-values 0.001 and 0.001, correspondingly). It was significantly decreased in the group of metformin than in the group of chromium (P-value=0.026) (Table 6).

Table (6): Fasting insulin level (milliunits per liter) between the groups of research

Time	Measure	Metformin (N=sixty)	Chromium(N=sixty)	^P-value (groups)
Pretreatment	**Mean ± SD**	15.3±4.1	15.1±3.7	0.77
	Range	3.4–22.5	3.2–22.1	
	N	38	42	
Month-3	**Mean ± SD**	11.6±3.2	13.1±3.5	0.015*
	Range	1.8–19.1	2.8–19.5	
Change (month 3 -pre)	**Mean ± SD**	-3.3±2.4	-1.7±3.3	0.002*
	Range	-10.2–2.9	-9.1–5.5	
#P-value (month three)		<0.001*	<0.001*	
Value of Metformin Relative to Chromium				
Items		**Mean ± SE**	**95% confidence interval**	
Insulin change		-1.7±0.5	-2.9–-0.3	

At follow-up, testosterone levels in both groups declined considerably compared to baseline (P-values 0.001 & 0.001, correspondingly), with no discernible variance among both groups (Table 7).

Table (7): Serum testosterone (picograms per milliliter) between the groups of study

Time	Measure	Metformin (N=sixty)	Chromium(N=sixty)	^P-value (groups)
Pretreatment	**Mean ± SD**	2.1±1.2	1.8±1.1	0.15
	Range	0.19–5.8	0.79–6.2	
	N	38	42	
Month three	**Mean ± SD**	1.5±0.4	1.4±0.9	0.43
	Range	0.4–3.1	0.21–3.3	
Change (month three pre)	**Mean ± SD**	-0.62±1.2	-0.38±0.50	0.15
	Range	-3.1–1.1	-3.1–0.21	
#P-value (month three)		<0.001*	<0.001*	
Value of Metformin Relative to Chromium				
Items		**Mean ± SE**	**95% confidence interval**	
Testosterone change		-0.11±0.21	-0.41–0.21	

According to adverse effects among the groups under research, there was no statistically significant variance among chromium group & metformin group regarding vertigo, headache, urticaria and taste disturbance (p=0.115, 0.166, 1 & 0.35 correspondingly). While, there was statistically significant difference between metformin group and chromium group regarding loss of appetite, abdominal discomfort, watery diarrhea, nausea and vomiting where (p=0.11, 0.020, 0.058, 0.004 & 0.009) correspondingly (Table 8).

Table (8): Side effects between the groups of study

Side effects	Metformin (N=sixty)	Chromium (N=sixty)	P-value	Relative rate(95% confidence interval)
Loss of appetite	3 (5%)	10 (17%)	#0.039*	0.26 (0.05–0.90)
Abdominal discomfort	12 (20%)	4 (7%)	#0.031*	3.19 (1.21–9.51)
Watery diarrhea	4 (7%)	1 (2%)	§0.170	--
Vertigo	6 (10%)	3 (5%)	#0.298	2.56 (0.79–9.74)
Headache	3 (5%)	6 (10.0%)	§0.298	0.23 (0.08–1.23)
Urticaria	3 (5%)	3 (5%)	§1.000	1.58 (0.30–8.80)
Nausea	12 (20.0%)	3 (5%)	#0.012*	4.56 (1.30–15.53)
Vomiting	10 (17%)	3 (5%)	#0.039*	5.6 (1.37–23.92)
Taste disturbance	2 (4%)	3 (5%)	§0.647	0.34 (0.03–2.28)

DISCUSSION

Chromium is an important mineral that plays an essential role in the metabolism of carbohydrates & lipids. Researchers have extensively researched chromium insufficiency as a potential treatment for hyperglycemia, particularly in cases of type two diabetes, due to its negative impact on glucose homeostasis and insulin resistance [8]. The medication is now recognized as a practical and reasonably priced therapeutic method [9]. **Tang *et al.*** [10] demonstrated that metformin is highly effective in stimulating ovulation and increasing pregnancy rates.

The current study showed that there was no significant variance among both groups concerning demographic characteristics (parity, age, & duration), and when compared to the baseline level at month three, BMI significantly fell in both groups (P-values 0.001 and 0.001, correspondingly), nonetheless non-significantly greater in the group of metformin than in the group of chromium (P-value = 0.062). The findings of our study are corroborated by **Amooee *et al.*** [3] who stated that there was no significance among the groups of study according to age and length. Also, **Rohaim *et al.*** [11] demonstrated that there was no significance among the groups of study according to age, parity, and BMI.

This study showed that according to progesterone in serum (ng/ml) within the groups under study, there was no statistically significant variance among the chromium group and the metformin group regarding pretreatment, month-1, change month-1-before, month-3, and change (month-1) (p = 0.09, 0.49, 0.055, 0.13, & 0.062) correspondingly. Our findings are corroborated by **Amooee *et al.*** [3] who stated that there was significance among the groups of studies according to progesterone in serum.

Also, **Rohaim *et al.*** [11] demonstrated that there wasn't significance among the groups of study according to progesterone in serum.

At months 1 and 3, the metformin group had a non-significantly higher ovulation rate than the chromium group (P-values, 0.26 and 0.157, respectively). Our findings are corroborated by **Amooee *et al.*** [3] who stated that there was significance among the groups of study according to ovulation detected by ultrasound, which happened in fifty-four (77.1%) individuals on metformin & forty-six (65.7%) instances taking chromium, according to **Haymond *et al.*** [12]. **Kishk *et al.*** [13] conducted a study with 60 PCOS patients and found that ovulation occurred in eleven (40.7%) of the metformin group's patients and twelve (44.4%) of the chromium group's patients. The variance among the two groups ovulation rates wasn't statistically significant (P-value = 0.134). The research by **Ashoush *et al.*** [6] involved eighty-five female PCOS patients (twenty–thirty-five years old) who received one thousand micrograms of CrP per day for six months. Ovulation was observed more frequently in the research group (one thousand micrograms of CrP/day) compared to the control group (placebo) following five months (n = twenty, 45.5% vs. n = eight, 19.5% P = 0.011) & six months (n = twenty-six, 59.1% vs. n = eight, 19.5% P below 0.001 correspondingly). The frequency of ovulation was significantly elevated by nearly two folds after five months (RR, 2.33; 95% confidence intervals: 1.16–4.69) & threefold following six months (RR, 3.03; 95% confidence intervals: 1.55–5.91).

This research showed that according to cumulative pregnancy among the groups of study, there was no statistically significant variance among the chromium group & the metformin group regarding Month-1, Month-2, and Month-3 (p = 0.999, 0.45, & 0.55) correspondingly. Also, **Rohaim *et al.*** [11] demonstrated that there was no any significance among the groups of research regarding cumulative pregnancy.

We found that concentrations of fasting blood glucose were considerably lesser in the metformin group than in the chromium group at follow-up compared to baseline (P-values & 0.001 correspondingly). Our findings are corroborated by **Amooee *et al.*** [3] who stated that there was significance among the groups of research regarding fasting blood glucose.

The current study showed that fasting insulin during the follow-up considerably lowered in each group related to level of baseline (P-values 0.001 and 0.001 correspondingly). It was significantly lower in the metformin group than in the chromium group (P-value = 0.026). At follow-up, testosterone levels in both groups declined considerably compared to baseline (P-values 0.001 & 0.001 correspondingly), with no discernible variance among a pair of groups. Our findings are corroborated by **Amooee *et al.*** [3] who stated that there was significance among the groups of research regarding fasting insulin.

Our findings showed that according to adverse effects among the groups under research, there was no statistically significant variance among the chromium group and the metformin group regarding vertigo, headache, urticaria, and taste disturbance (p = 0.151, 0.166, 1 & 0.35 correspondingly). While, there was a statistically significant variance among the metformin group & the chromium group regarding loss of appetite, abdominal discomfort, watery diarrhea, nausea, and vomiting (p = 0.11, 0.020, 0.058, 0.004, & 0.009 correspondingly). According to **Amooee *et al.*** [3], patients who took metformin had higher adverse effects than those who received chromium picolinate. Also, **Rohaim *et al.*** [11] demonstrated that there was no significance among the groups

of study according to nausea and vomiting. Furthermore, metformin treatment was correlated to a greater frequency of nausea (P = 0.028), indigestion (P = 0.039), diarrhea (P = 0.001), vomiting (P = 0.001), & abdominal pain (P = 0.002), whereas chromium picolinate was correlated with headache (P = 0.001) & lack of appetite (P = 0.018) [14].

CONCLUSION

According to the results above, we advise some PCOS patients to switch from metformin to chromium picolinate because it was less likely to cause side effects, was better tolerated, and did not significantly differ from the other group regarding ovulation and pregnancy rates.

DECLARATIONS

- **Consent for publication:** Authors granted permission for the work to be submitted.
- **Funding:** No fund.
- **Availability of data and material:** Available.
- **Conflicts of interest:** No conflicts of interest.
- **Competing interests:** None

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