



## **PROTOCOL OF A THESIS FOR PARTIAL FULFILMENT OF MASTER DEGREE IN OBSTETRICS & GYNAECOLOGY**

**Title of the Protocol: The Efficacy of Using Chromium Salts in Reducing Hirsutism Scoring & BMI in Polycystic Ovary Syndrome Patients A Randomized Controlled Trial**

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**What is already known on this subject? AND**

**What does this study add?**

The polycystic ovary syndrome (PCOS) is the most common gynecological endocrinopathy among women in reproductive age. The prevalence of PCOS among such women is estimated to be 6.4% to 6.8% worldwide (*Azziz et al., 2004*). PCOS is characterised by hyperandrogenism and chronic anovulation (*Kelly, 2000*). In the etiopathogenesis of PCOS, the role of insulin resistance is emphasized as minimizing insulin resistance can play a significant role in controlling PCOS (*Moggetti, 2016*) which was an indication for the attempts at using chromium III salts (Cr) in augmenting pharmacotherapy applied in patients. The analysis of the usefulness and efficacy of this approach was the direct goal of this thesis.

## 1. INTRODUCTION/ REVIEW

Polycystic ovary syndrome (PCOS) is one of the most frequent endocrinopathies in women in reproductive age and in adolescence. The causes of PCOS are still being studied; there is an ongoing search for the genes responsible for the manifestation of the disease, and the clinical image is extraordinarily heterogeneous. There are gynecological and metabolic symptoms; all of them influence patient's psychological condition and self-esteem (*Kurek, 2017; Cooney, 2017*).

PCOS is defined by having at least 2 of the following criteria: irregular or absent ovulation, elevated levels of androgenic hormones and enlarged ovaries containing at least 12 follicles each (*Rotterdam ESHRE/ASRM, 2004*). The use of the broader ESHRE/ ASRM 2003 criteria was encouraged, but accompanied with a detailed description of the PCOS phenotype included. the NIH consensus panel recommended use of the following phenotype classification:

- Phenotype A: Hyperandrogenism (clinical or biochemical presence) + Ovulation dysfunction + Polycystic ovary morphology
- Phenotype B: Hyperandrogenism + Ovulation dysfunction
- Phenotype C: Hyperandrogenism + Polycystic ovary morphology
- Phenotype D: Ovulation dysfunction + Polycystic ovary morphology (*Azziz R, 2006*)

( Phenotypes A , B and C with hyperandrogenism are the main concern in this thesis)

Hyperandrogenism manifests by androgenic alopecia, hirsutism, acne lesions, increased hair loss, oily skin, seborrhoeic lesions and clitoromegaly. Hirsutism, one of the most frequent symptoms, assessed according to the Ferriman–Gallwey score, is the presence of gruff, thick and pigment-saturated hair in women in places typical for men, e.g. upper lip, chin, chest, nape of the neck, lumbar region, abdomen, thighs and feet (*Bumbuliene, 2009*). A frequently appearing skin symptom in women with PCOS is also acanthosis nigricans,



usually located on elbows, nape of the neck, armpits and under breasts (*Housman, 2014; Dong, 2013*). The increased insulin levels found in patients with PCOS appear to directly enhance LH stimulated androgen secretion from the ovary (*Nestler, 2001*).

Androgens are the key factors in the growth and development of sexual hair. Androgens act on sex-specific areas of the body, converting small, straight, fair vellus hairs to larger, curlier, and darker terminal hairs (*Rosenfield, 2005*). Hirsutism is very common and often improves with medical management. Prompt medical attention is important because delaying treatment makes the treatment more difficult and may have long-term health consequences.

More than half of the women suffering from PCOS experience overweight and obesity, usually of the androidal type (*Joham, 2015*). Increased body weight has negative influence on carbohydrate economy, which causes insulin resistance, leading also to hyperinsulinaemia. It is thought that high concentration of circulating insulin contributes to the increased production of androgen in an ovary and to ovulation disorders. In a significant part of patients, an abnormal lipid profile is observed. Patients with PCOS are at high risk of developing cardiovascular disease being its distant consequence (*Kuligowska 2012; Spritzer, 2014*).

Metformin has been used for PCOS treatment since 1994 (*Velazquez EM, 1994*) by which most of the metabolic abnormalities of PCOS can be reversed (*Moggetti P, 2000*). The mechanism is thought to be mediated through increased insulin sensitivity, increased ovarian secretion of estrogen, decreased ovarian production of androgen and augmentation of the production of sex hormone binding globulin (*Glueck CJ, 2001*).

Because up to 70% of patients with PCOS demonstrate overt insulin resistance and hyperinsulinism with dyslipidemia, the administration of insulin-sensitizing agents, principally metformin has been proposed for the treatment of hirsutism. These agents have various potential advantages over traditional therapies: they correct both the metabolic and the endocrinologic aberrations of the disorder; they permit the resumption of normal endogenous ovulatory function, with little or no risk of ovarian hyperstimulation and multiple gestation; and they may possibly decrease the long-term risk of type 2 DM and CVD. (*Velazquez EM, 1994*)

In patients with PCOS, obesity and dyslipidemia are more frequent (*Joham, 2015*). This led to the hypothesis that the application of supplementation with chromium (III) which is the synthetic salt form of Cr chloride which is the naturally occurring trivalent variety of chromium found in common food as broccoli, mushrooms and green beans. Piclonic acid may serve to improve chromium absorption (*Yin and Phung, 2015*). Adequate intake (AI) was set based on estimated mean intakes and amounts 35 µg/day and 25 µg/day for young men and women, respectively. It is indicated as a microelement facilitating in maintaining normal glycaemia by activating insulin signal transduction and sensitivity and normal level of lipoprotein in plasma and dealing with obesity (*Piotrowska, 2018*).

Minimizing insulin resistance can play a significant role in controlling PCOS (*Moggetti, 2016*). The development and understanding of the phenomenon of insulin resistance in the pathogenesis of this syndrome were an indication to search for new methods,



including adjusting the diet of patients. One of the methods leading to this effect was supposed to be chromium (III) (*Geller, 2011*).

## 2. AIM / OBJECTIVES

### The aim of this study is to

This study is designed to assess the effect of chromium salts in decreasing hirsutism scoring & Body Mass Index in polycystic ovary syndrome patients.

### Research question:

Does applying chromium salts will decrease hirsutism scoring and body mass index in polycystic ovary syndrome patients?

### Research Hypothesis

In this current study, we hypothesize that adding chromium salts to ordinary treatment will decrease hirsutism scoring and body mass index in polycystic ovary syndrome patients.

### Primary outcomes

To correlate between hirsutism scoring with adding chromium salts as a supportive agent in polycystic ovary syndrome patients

**Decrease in hirsutism scoring in chromium group by  $1.8 \pm 2.5$  compared to placebo group (*Jamilian, 2015*).**

### Secondary outcomes

#### ➤ Effect on BMI

Body weight was measured using analogue scales in light clothes; height was measured barefoot using a stadiometer. Body mass index was calculated as follows: weight (kg)/height<sup>2</sup> (m).

Anthropometric measurements were made using standard techniques; waist circumference was obtained as the minimum value between the iliac crest and the lateral costal margin, whereas hip circumference was determined as the maximum value over the buttocks.

#### ➤ Regulation of menses

The patient would be asked about her menstrual history (time between cycles, frequency, duration)

#### ➤ Side effects of chromium salts

Trivalent chromium is an essential trace element that is considered safe when ingested in normal quantities so, Side effects following proper administration of therapeutic dose are not recorded but it may include: Insomnia, Mood

changes, Irritability and Headache .so , patients should be asked about this side effects.

➤ **Side effects of metformin**

Metformin is an established treatment with a good safety profile (**DeFronzo RA,1999**). Along with its needed effects, metformin may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention which include:

Abdominal or stomach discomfort, cough or hoarseness, decreased appetite, Diarrhea ,fast or shallow breathing ,fever or chills ,general feeling of discomfort ,lower back or side pain muscle pain or cramping, sleeping, Anxiety, blurred vision ,chest discomfort ,cold sweats, coma ,confusion cool pale skin depression ,difficult or labored breathing, dizziness, headache ,increased hunger ,increased sweating ,nausea, nervousness Nightmares, redness of the face, neck, arms, and occasionally, upper chest and seizures.

These symptoms occur with variable degrees in patients and in most cases resolve spontaneously. So, patients should be asked about this side effects .

### 3. Methodology:

#### Patients and Methods/ Subjects and Methods/ Material and Methods

- **Type of Study:** Double blinded Randomized Controlled clinical Trial.
- **Study Setting:** The study will be conducted in Ain Shams university Hospital on polycystic ovary syndrome patients attending outpatient clinic.
- **Study Population:** Polycystic ovary syndrome patients with hyperandrogenism attending outpatient clinic.
- **Sample Size:** Pilot study will be done on 30 patients per group.
- **Sampling method:** Systematic random sample
- **Duration of the study:** the study will be done within 4 months.
- **Sample Justification:** No available literature for sample size calculation so this is considered as a Pilot study that will be done on 30 patients per group.
- **Ethical Considerations:** After approval of Research Ethical Committee, faculty of medicine of Ainshams University ,the clinical research study will be conducted. Informed written consent will be taken .
- **Study Procedures:** This study will be conducted in Ain Shams University maternity hospital outpatient clinic.

the study will be conducted on (60) women diagnosed as having polycystic ovary syndrome with hyperandrogenism.

On their visit to the clinic, PCOS patients to be selected and to be counseled and consented to participate in the study

Women will be distributed into 2 groups but, Both groups would receive metformin with dose of 500mg after main meal

The two groups would be:

Group (S) (study): (n=30) chromium (**chromium picolinate, Mepaco**) will be given orally in a dose of 200 microgram/day for 4 months duration.

Group (C) (control): (n=30) will receive placebo ) in the form of c retard capsules).

### **Inclusion criteria**

1- Cases of PCOS syndrome according to Rotterdam criteria: PCO syndrome could be diagnosed after exclusion of related disorders by 2 of the following 3 features:

- Oligo or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries by ultrasound features: Bilateral enlarged ovaries with multiple small follicles with
  - Increased ovarian volume (<10cc)
  - 12 or more follicles measuring (2-9mm)
  - Follicles of similar size
  - Peripheral location of the follicles which can give a string of pearl appearance
  - Hyperechoic central stroma, thick cortex
  - The ovarian outline may be slightly irregular

2- Accept to participate and provide consent.

3- Females between 18-40 years of age with hirsutism.

### **Exclusion criteria**

The patients with any of the following criteria are excluded from the study:

- 1- Patient unwilling or unable to provide consent
- 2- Female age <18years and >40years
- 3- Patients known to be diabetic or hypertensive.
- 4- Patients receiving corticosteroids, psychotropic drugs, diuretics
- 5- Ovulation induction
- 6- Usage of permanent method of hair removal.

**Both groups would undergo:**

- Lifestyle intervention (preferably multicomponent including diet , exercise and behavioral strategies) (*Teede HJ., 2018*)

To achieve weight loss in those with excess weight, an energy deficit of 30% or 500-750 kcal/day (1,200 to 1,500 kcal/day) could be prescribed for women, also considering individual energy requirements, body weight and physical activity levels. (*Teede HJ., 2018.*)

Health professionals should encourage a minimum of 150 min/week of moderate intensity physical activity or 75 min/week of vigorous intensities or an equivalent combination of both, including muscle strengthening activities on 2 non-consecutive days/week (*Teede HJ., 2018*).

Behavioral strategies such as goal-setting, self-monitoring ,stimulus control, problem solving, assertiveness training, slower eating, reinforcing changes and relapse prevention, to optimize weight management, healthy lifestyle and emotional wellbeing in women with PCOS.( (*Teede HJ., 2018*).

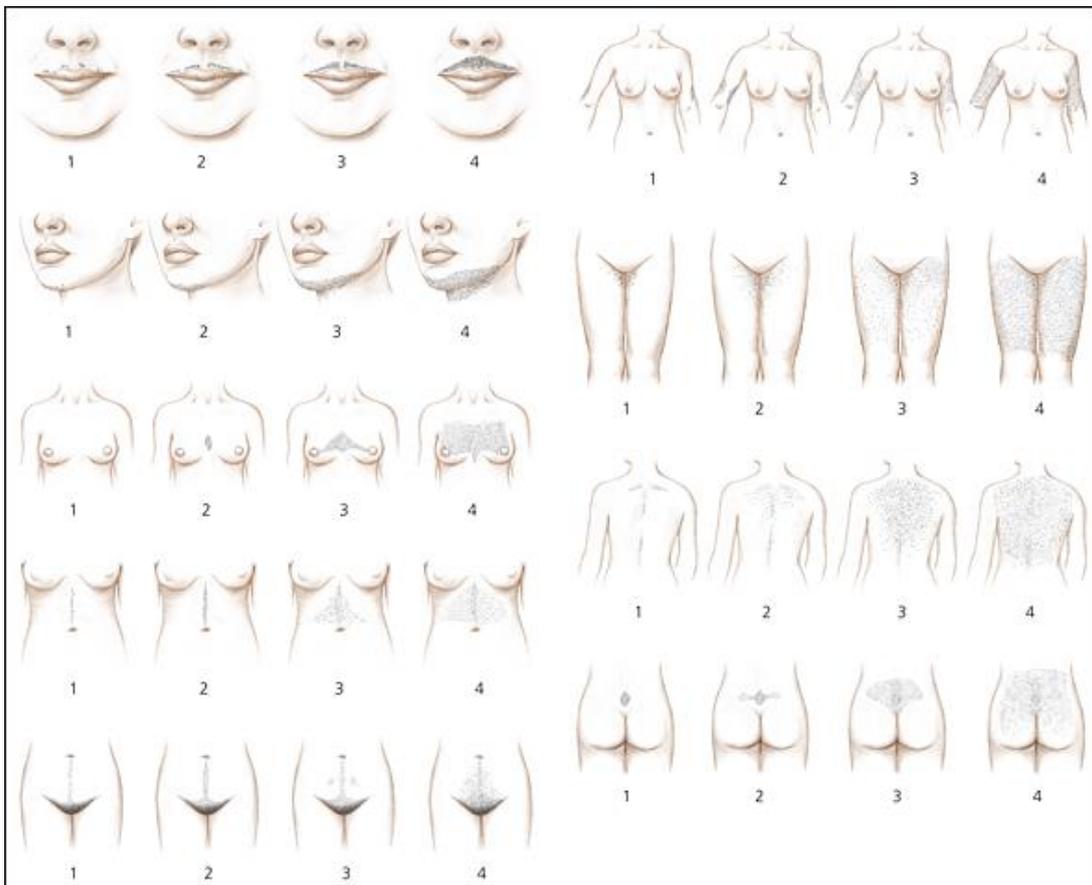
- would receive metformin with dose of 500mg after main meal.
- **Randomization:** Closed opaque envelop method...as thirty envelops would contain chromium and another thirty envelops would contain placebo mixed together not known by the examiner nor the patients only known by the nurse in the outpatient clinic and she would choose each envelop for each patient.
- **Method of allocation:** Closed opaque envelop method.
- **Blinding:** Double blinded randomized controlled clinical trial.

**All the participants will be subjected to the following:**

- 1- Written informed consent
- 2- History taking
  - Personal history: name, age, occupation, marital status &duration, residency, habits of medical importance and husband full history
  - History of the present illness: duration of infertility, history of investigations and treatment.
  - Menstrual history: criteria & average number of menses for year and last normal menstrual period.
  - Past history: medical and surgical history.
  - Family history: of similar condition.
  - Sexual history: frequency, regular unprotected sexual intercourse, pain

3- Physical examination: measurement of BMI

4- General examination: For hirsutism Physical examination should begin with determination of the distribution and degree of hair growth using a scoring method such as the Ferriman-Gallwey scale (according to the Ferriman–Gallwey score. A score of 1 to 4 is given for nine areas of the body. A total score less than 8 is considered normal, a score of 8 to 15 indicates mild hirsutism, and a score greater than 15 indicates moderate or severe hirsutism. A score of 0 indicates absence of terminal hair (*Yildiz et al., 2010*).



5- Abdominal examination.

6- Skin examination: should check for acne or acanthosis nigricans.

**Follow Up:** Along with Dietary control and Exercise performing encouragement, the patients would be followed up for taking the drug regularly by phone calls every two weeks.

Also, it would be for the frequency of hair removal every month for **4 months durations** with usage of temporary method of hair removal and to be stopped before follow up date by 2 weeks.

**Efficacy and toxicity of combined metformin and chromium salts:** Pharmacologic dosages of chromium (200 mcg/day or more for adults) may help improve diabetic control



and reduce the requirements for insulin and other antidiabetic agents. Chromium appears to play a role in normal insulin function and glucose utilization, and some investigators have suggested that it increases insulin sensitivity and glucose tolerance and decreases blood glucose levels in certain diabetics, possibly those with low chromium levels. (*Anderson RA,1998*) However, others have not corroborated these findings, and a few have even reported a negative effect on glucose tolerance and blood levels so, Until further data are available, therapy with pharmacologic dosages of chromium should be administered cautiously in patients receiving insulin or other antidiabetic agents. Patients should be monitored for changes in medication requirements. (*Martin J,2006*)

In a study done before, the use of 1000 mcg/day of chromium picolinate in 180 type 2 diabetic patients for a period of four months showed no toxic reactions in any of the patients. (*Anderson RA,1997*)

If the patient couldn't tolerate either drugs she would be dropped from the study.

○ **Statistical Analysis:**

Analysis of data will be done by SPSS program version 23 using the appropriate statistical tests.



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