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N-Acetyl Cysteine, Chromium Picolinate: Adjuvant to Clomiphene Therapy of PCOS

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Abstract

Aim of the work

The purpose of this study was to compare the efficacy and safety of clomiphene citrate (CC) alone versus CC plus N-acetyl cysteine (NAC) and CC plus chromium picolinate (CrP) in management of PCOS.

Patients and Methods

This study, accomplished on 120 women with PCOS and fulfilling Rotterdam criteria 2003. Patients were divided into three equal groups; the First Group (n=40) given out NAC plus CC. The second group (n=40) administered CrP plus CC. The last group (n=40) dispensed CC alone.

Results

The number of follicles (≥18 mm), mean endometrial thickness on the day of hCG administration and number of pregnancies were higher among PCOS cases given NAC+CC group than CrP+CC and CC alone cases. No adverse side-effects and one case of ovarian hyperstimulation syndrome observed in the group receiving CC+NAC.

Conclusion

NAC is a safe and well-tolerated adjuvant to CC. It improves follicular maturation and pregnancy rate in PCOS patients. In addition, chromium picolinate does not improve follicular maturation or pregnancy rate when added to CC in women with PCOS.

Introduction

Polycystic ovary syndrome (PCOS) constitutes a continuum spectrum of symptoms starting from the early prepubertal years and continuing after menopause. The phenotypic expression varies through time, depending on several internal (e.g. ovarian/adrenal steroidogenesis, insulin resistance) and external factors (e.g. quality and quantity of food, exercise). To a great extent, etiology of PCOS has remained unknown although it has been revealed that synthesis of high levels of androgen, and insulin-resistance (IR) lies at the core of its pathophysiology [1].

In 2003, another conference of experts was organized in Rotterdam. The meeting recommended that PCOS be defined when two of the following three features are present: oligo or an ovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries found on ultrasound. Per the Rotterdam criteria, ultrasonographic evidence of polycystic ovaries is either by ovarian volume in one or two ovaries >10 cm^3 and/or a follicle count (2–9 mm) of ≥12 follicles. [2] PCOS is considered to be the most prevalent endocrinopathy resulting from an ovulation. [3] PCOS affects approximately 5-10% of the women in the reproductive age [4].

The recommended first-line treatment for ovulation induction in women with PCOS remains clomiphene citrate. Recommended second-line intervention, should CC fail to result in pregnancy, are either exogenous gonadotropins or laparoscopic ovarian surgery. Recommended third-line treatment is in vitro fertilization (IVF) [5].

Few years ago, until now, there was an interest in the use of insulin-sensitizing drugs in women with PCOS. In a good percentage of cases, treatment with these drugs is followed by an improved response to therapies for induction of ovulation. Several insulin-lowering drugs have been introduced in the management of PCOS. These drugs include metformin, thiazolidine and N-acetyl cysteine and others [6].

N-acetyl cysteine is commonly used as a safe mucolytic drug. NAC has been shown to influence both the insulin secretion in pancreatic β-cells, as well as the regulation of insulin receptors in human erythrocytes. [7] Moreover, NAC has antioxidant effects via increasing the cellular levels of reduced glutathione. [8,9] In addition, NAC has a preventive effect on the endothelial damage in non-insulin dependent diabetic subjects [8]. In recent years, a limited number of studies have shown the possible benefits of NAC administration in improving induction of ovulation outcomes in patients with PCOS [10,11].

Chromium picolinate is a chemical compound sold as a nutritional supplement to prevent or treat chromium deficiency. This compound is derived from chromium and picolinic acid. Small quantities of chromium are needed for glucose utilization by insulin in normal health, but deficiency is extremely rare. No biochemical basis for the human body's need for chromium has been identified [12].

Chromium (III) tris (picolinate) (CrPic) is a bio-available form of Cr (III) that is a popular dietary supplement that is not regulated by the Food and Drug Administration. [13] In 2010, chromium picolinate was approved by Health Canada to be used in dietary supplements [14].

The present study pursued the efficacy and safety of N-acetyl cysteine as an adjunct to clomiphene citrate, chromium picolinate as an adjunct to clomiphene citrate (CC) and CC alone in management of PCOS.

Patients and Methods

This cohort study carried out on 120 women recruited from attendants of the department of Obstetrics and Gynecology of Tanta University, Tanta, Egypt. Recruitment began in March 2013 and was completed in December 2013. All patients had PCOS diagnosed by Rotterdam's criteria. Patients were divided into three equal groups; the members of the first group (n=40) were given clomiphene citrate plus N-acetyl cysteine. The members of the second group (n=40) were given clomiphene citrate plus chromium picolinate. The members of the third group (n=40) were given clomiphene citrate alone.

• **Inclusion criteria:** Participants were to be included if they have if they were less than 35 and older than 18 years old, and if they had a body mass index between 25and <30, and with primary infertility for ≥ 2years.

• **Exclusion criteria:** Patients with history of prior induction of ovulation, male factor of infertility, tubal factor infertility and/or uterine factor infertility, history of previous medical disorders, abdominal or pelvic surgery, dental & oral diseases and cases with history of T.B. or any other systemic diseases.

The protocol of this study was approved by the ethical committee of our institution. All patients included in the study were counseled thoroughly about the procedure, including its value and hazards, and the aim of the study. After this, a written consent was obtained and signed by the patient. We did not classify the patients according to their religion or culture or race or any other unrelated points. The next steps were done for every case: history taking, clinical examination, and transvaginal ultrasonographic examination. Estimation of serum levels of FSH and LH was done by radioimmunoassay on the third day of the menstrual cycle.

Using a computer-based random digit generator, study participants were randomly assigned to three treatment groups for ovulation induction. The 40 participants assigned to group 1 received 100 mg of clomiphene citrate on cycle day 3–7 along with 1,200 mg of N-acetyl cysteine (*Acetylcystein 600 Effervescent instant sachets, 600 mg/sachet – Sedico, Egypt*). The 40 participants assigned to group 2 received 100 mg of clomiphene citrate on cycle day 3–7 along with a 1000 µg of Chromium picolinate 200 µg / tablet (*NutraChrom, Jedico, Egypt*). The 40 participants assigned to group 3 received 100 mg of clomiphene citrate from day 3 until day 7 of the cycle (*Clomid 50 mg/tablet of Sanofi-Aventis*).

Participants were monitored by transvaginal ultrasound for the number of mature follicles (defined by a diameter ≥ 18 mm), and thickness of the endometrium on days 10, 12, and 14 of the cycle. An intramuscular injection of 10,000 units of human chorionic gonadotropin (hCG) was administered for timed intercourse was advised 24-36 hours after hCG injection. In addition, serum β-hCG was measured 16 days after the hCG injection for confirmation of a positive pregnancy test.

Treatment had continued to one cycle, and the primary outcome measures were number of mature follicles (>18 mm) in the ovary, endometrial thickness and serum insulin levels (a fasting insulin of 10-13 mIU/ml generally indicates some insulin resistance). Secondary outcome measure was the occurrence of pregnancy.

Statistical analysis of the results was performed by using statistical software program SPSS V.16. [15] We also used the Henry Scheffé test to determine which means or combination of means differed significantly from which other means or combination of means in an analysis of variance when the overall F ratio for those means in that analysis was significant and when such differences had not been predicted prior to the analysis as it is suitable for groups of unequal size.

Results

The results of this investigation are depicted in four tables:

• Table (1): It displays that the three studied groups were well matched concerning age and body mass index and duration of infertility, there was no statistical significance between the three groups.

• Table (2): It depicts no statistically significant differences in FSH/LH ratio between the three studied groups. In addition, this table shows that fasting serum insulin levels at the day of hCG injection in studied groups.

• Table (3): It validates that administration of N-Cysteine plus clomiphene citrate (Group-1) significantly increased the number of ovarian mature follicles (follicles measuring ≥18 mm in diameter) compared to those receiving clomiphene citrate alone. Similarly, the number of mature follicles among women receiving chromium picolinate plus clomiphene citrate (Group-2) was significantly higher than that of women receiving clomiphene citrate only. However, considering the number of mature follicles, the difference between group 1 and 2 was insignificant (P=0.096). The mean endometrial thickness on the day of hCG administration was significantly taller among patients of group-1 compared to those of group-2.

• Table (4): It demonstrates that there was a statistically significant increase in pregnancy rate in group 1 (after administration of NAC+CC) than the other two groups.

Table 1: Age, BMI and duration of infertility in the studied groups

Age distribution:			
Age in years	Group 1	Group 2	Group 3
Range	25-31	28-30	24-30
Mean ± SD	27.8±2.36	27.2±1.77	27.7±2.21
P vale	0.89827		
		0.86545	
	0.42255		
Body Mass index:			
BMI	Group 1	Group 2	Group 3
Range	21.6-24.56	23.53-25.47	22.32-25.3
Mean ± SD	22.78±1.01	24.54±0.82	23.64±1.35
P vale	0.39904		
		0.55158	
	0.44978		
Duration of infertility:			
Duration in years	Group 1	Group 2	Group 3
Range	2-4	2-6	3-5
Mean ± SD	3.63±0.79	4.20±1.50	3.92±0.63
P vale	0.4193		
		0.53913	
	0.45798		

Group 1 = patients given (NAC+CC); Group 2= patients given (CrP+CC)
Group 3 = patients given (CC alone); SD= standard deviation

Table 2: LH/FSH and fasting insulin levels in studied groups

LH/FSH levels on day 3 of the cycle in the studied groups:			
LH/FSH	Group 1	Group 2	Group 3
Range	1.97-2.2	2-2.6	1.8-3
Mean	2.15±0.08	2.20±0.25	2.30±0.59
Scheffé's test			
	G1 Versus G2	G1 Versus G3	G2 Versus G3
P value	0.632	0.253	0.280
Fasting insulin levels at the day of hCG injection in studied groups:			
Fasting insulin	Group 1	Group 2	Group 3
Range	18.5-26.5	0-26.1	0.1-1
Mean	17.63±3.51	21.52±6.35	0.65±.0.14
Scheffé's test			
	G1 Versus G2	G1 Versus G3	G2 Versus G3
P value	0.006	0.006	0.006

Group 1 = patients given (NAC+CC); Group 2= patients given (CrP+CC)
Group 3 = patients given (CC alone); SD= standard deviation
LH = Luteinizing hormone, FSH = Follicle stimulating hormone

Table 3: Number of mature follicles (measuring ≥ 18mm in diameter) among the studied groups

Number of mature follicles (measuring ≥ 18mm in diameter)			
Follicles number:	Group 1	Group 2	Group 3
Range	0-2	2-3	0-1
	1.63±0.42	2.40±0.49	0.58±0.12
Scheffé's test			
	G1 Versus G2	G1 Versus G3	G2 Versus G3
P Value	0.096	0.003	0.001
Endometrial thickness			
Endometrial thickness in mm	Group 1	Group 2	Group 3
Range	5.3-8.3	5.3-8.1	5.4-7.5
	6.98±1.16	5.28±0.9	6.12±0.78
Scheffé's test			
	G1 Versus G2	G1 Versus G3	G2 Versus G3
P value	0.005	0.030	0.636

Group 1 = patients given (NAC+CC); Group 2= patients given (CrP+CC)
Group 3 = patients given (CC alone); SD= standard deviation

Table 4: Comparison of pregnancy rate between the study groups

Group 1 (N=40)		Group 2 (N=40)		Group 3 (N=40)	
No of Pregnancies	%	No of Pregnancies	%	No of Pregnancies	%
5	12.5	2	5	1	2.5

Group 1 = patients given (NAC+CC); Group 2= patients given (CrP+CC)
Group 3 = patients given (CC alone)

Discussion

N-Acetyl cysteine is the acetylated variant of the amino acid L-cysteine. It is an excellent source of sulfhydryl groups and is converted in vivo into metabolites that stimulate glutathione production, promote detoxification, and act directly as free-radical scavengers. It is primarily a powerful antioxidant; [16] it has activity on insulin secretion in pancreatic cells and on insulin receptors on human erythrocytes [17].

Animal studies proved that the drug is neither teratogenic nor mutagenic. [18] Because it is an insulin sensitizer, NAC was proposed as an adjuvant to clomiphene citrate for ovulation induction in patients with polycystic ovary syndrome. Bedaiwy et al. [19] used NAC for ovulation induction in unexplained infertility while Rizk et al. showed the efficacy of NAC plus CC in treatment of an ovulation in polycystic ovary syndrome. [11] The present study demonstrated that administration of NAC plus clomiphene citrate significantly increased the number of mature follicles.

The number of follicles >18mm and the mean endometrial thickness on the day of hCG administration were significantly higher among the NAC+CC group. This matches with the results of Salehpour and others [20].

The current investigation illustrated that adjunct NAC to clomiphene citrate therapy improved conception rate. This agrees with the results of Badawy et al. [21] This improved conception rate may be attributed to the fact that N-acetyl cysteine improve cervical mucus quality [22].

Ovulation rate improved significantly after the addition of N-acetyl cysteine (17.9% versus 52.1%). Although the number of mature follicles was more in the N-acetyl cysteine group (2.1±0.88 versus 3.2±0.93), the difference was not statistically significant. Authors concluded that N-Acetyl cysteine is proved effective in inducing or augmenting ovulation in polycystic ovary patients [21].

Trivalent chromium is an essential element that plays a role in glucose and insulin homeostasis. Chromium deficiency as a cause of glucose intolerance was recognized first in 1977, when a trauma patient receiving total parenteral nutrition developed severe diabetes refractory to insulin. Symptoms completely resolved when chromium chloride was added to the total parenteral nutrition [23].

Until recently, not much was known about the mechanism of chromium action other than that it appeared to improve the effects of insulin and worked at the level of the cell membrane. [24] The interaction between chromium and insulin has been elucidated by the discovery of low–molecular weight chromium-binding substance, which binds chromium and the insulin receptor, activating the insulin receptor's kinase activity [25].

In women with polycystic ovary syndrome, chromium picolinate (200µg/d) improves glucose tolerance compared with placebo but does not improve ovulatory frequency or hormonal parameters [26].

The contemporaneous study determined that administration of chromium picolinate in addition to clomiphene citrate increased significantly the number of mature follicles in the ovaries. Moreover, administration of chromium picolinate coupled with clomiphene citrate increased the pregnancy rate among women with PCOS. However, the effects of chromium picolinate plus clomiphene citrate were less than those of N-acetyl cysteine plus clomiphene citrate.

Disclosure

We declare that we have no conflict of interests with anybody. Moreover, we declare that we did not receive any funds from any person or institution.

References

1. Livadas S, Diamanti-Kandarakis E (2013) Polycystic ovary syndrome: definitions, phenotypes and diagnostic approach. Front Horm Res 40:1-21.
2. Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group (2014) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Hum Reprod 19: 41-47.
3. Homburg R (2008) Polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol 22: 261-274.
4. Parsanezhad ME, Alborzi S, Zarei A, Dehbashi S, Omrani G (2001) Insulin resistance in clomiphene responders and non-responders with polycystic ovarian disease and therapeutic effects of metformin. Int J Gynaecol Obstet 75: 43-50.

5. (1994) ACOG technical bulletin: Managing the anovulatory state: Medical induction of ovulation. Number 197 September 1994. Committee on Technical Bulletins of the American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 47: 305-312.
6. De Leo V, La Marca A, Petraglia F (2003) Insulin-Lowering Agents in the Management of Polycystic Ovary Syndrome. Endocr Rev 24: 633-667.
7. Santini MT, Cametti C, Indovina PL, Peterson SW (1998) Menadione induces changes in the membrane electrical properties associated with down-regulation of insulin receptors in human erythrocytes. Exp Hematol 26: 466-471.
8. Borgström L, Kågedal B, Paulsen O (1986) Pharmacokinetics of N-acetylcysteine in man. Eur J Clin Pharmacol 31: 217-222.
9. Wentzel P, Thunberg L, Eriksson UJ (1997) Teratogenic effect of diabetic serum is prevented by supplementation of superoxide dismutase and N-acetylcysteine in rat embryo culture. Diabetologia 40: 7-14.
10. Fulghesu AM, Ciampelli M, Muzj G, Belosi C, Selvaggi L, et al. (2002) N-acetyl-cysteine treatment improves insulin sensitivity in women with polycystic ovary syndrome. Fertil Steril 77: 1128-1135.
11. Rizk AY, Bedaiwy MA, Al-Inany HG (2005) N-acetyl-cysteine is a novel adjuvant to clomiphene citrate in clomiphene citrate resistant patients with polycystic ovary syndrome. Fertil Steril 83: 367-370.
12. Stearns DM (2000) Is chromium a trace essential metal? Biofactors 11: 149-162.
13. Stearns DM, Silveira SM, Wolf KK, Luke AM (2002) Chromium (III) tris (picolinate) is mutagenic at the hypoxanthine (guanine) phosphoribosyltransferase locus in Chinese hamster ovary cells. Mutat Res 513: 135-142.
14. Vincent JB (2010) Chromium: celebrating 50 years as an essential element? Dalton Trans 39: 3787-3794.
15. Bland M (2000) An Introduction to Medical Statistics, 3rd Edition. Oxford University Press, London.
16. Mitwally MF, Biljan MM, Casper RF (2005) Pregnancy outcome after the use of an aromatase inhibitor for ovarian stimulation. Am J Obstet Gynecol 192:381-386.
17. Flughesu AM, Ciampelli M, Muzj G, Belosi C, Selvaggi L, et al. (2002) N-acetyl cysteine treatment improves insulin sensitivity in women with polycystic ovary syndrome. Fertil Steril 77: 1128-1135.
18. Threlkeld DS (1997) Drug facts and comparisons. St Louis, Missouri: Facts and Comparisons 23: 1090-1094.
19. Jeejeebhoy KN, Chu RC, Marliss EB, Greenberg GR, Bruce-Robertson A (1997) Chromium deficiency, glucose intolerance, and neuropathy reversed by chromium supplementation, in a patient receiving long-term total parenteral nutrition. Am J Clin Nutr 30: 531-538.
20. Salehpour S, Sene AA, Saharkhiz N, Sohrabi MR, Moghimian F (2012) N-acetylcysteine as an adjuvant to clomiphene citrate for successful induction of ovulation in infertile patients with polycystic ovary syndrome. J Obstet Gynaecol Res 38: 1182-1186.
21. Badawy A, State O, Abdelgawad S (2007) N-Acetyl cysteine and clomiphene citrate for induction of ovulation in polycystic ovary syndrome: a cross-over trial. 86: 218-222.
22. Bedaiwy MA, Rizk A, Inany AH, Falcone T (2004) N-acetylcysteine improves pregnancy rates in long standing unexplained infertility: a novel mechanism of ovulation induction 82: S228-S262.
23. Bateman BG, Nunley WC Jr ,Kolp LA (1990) Exogenous estrogen therapy for treatment of clomiphene citrate induced cervical mucus abnormalities: is it effective? Ferti Steril 54:577-9.
24. Mertz W (1998) Chromium research from a distance: from 1959 to 1980. J Am Coll Nutr 17: 544-7.
25. Vincent JB (1998) Mechanisms of chromium action: low-molecular-weight chromium-binding substance. J Am Coll Nutr 18: 6-12.
26. Lucidi RS, Thyer AC, Easton CA, Holden AE, Schenken RS, et al. (2005) Effect of chromium supplementation on insulin resistance and ovarian and menstrual cyclicity in women with polycystic ovary syndrome. Fertil Steril 84: 1755-1757.