Research High Lights

Efficacy of Cabergoline Combined with Letrozole Versus Letrozole Alone in Anovulatory Pco Women with Europrolactinaemia, Randomized Controlled Trial

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ABSTRACT

Objective: To evaluate the therapeutic effect of adding cabergoline with letrozole in infertile women having polycystic ovarian syndrome (PCOS) with normal serum prolactin level.

Study Design: A randomized controlled study.

Patients & Methods: Infertile anovulatory PCOS women with normal prolactin level attending out patient clinic of obstetric &gynaecology department of zagazig university and private clinic . Those included(200) patients were randomly divided into two groups each group with (100) patients, where group A,received letrozole plus cabergoline and group B recieved letrozole.

Study Design: For all patients included,basal ultrasound on 2nd day of cycle before medication administration,,,,group (I) letrozole plus cabergoline group , Letrozole (2 tablets) 5mg oral daily from cycle day 3 of spontaneous or progestin induced cycle for 5days plus cabergoline (Dostinex® tablet), 0.25 mg once weekly for 4 week starting from cycle day 3 with letrozole. Group (II) receive letrozole 5mg(2tablet)oral only from cycle day 3 of spontaneous or progestin induced cycle for 5days. then folliculometry was done detecting number,size of ovarian follicles ≥17mm with corresponding endometrial thickness ,patients followed for one cycle. The primary outcome was ovulation rate in both groups. The secondary outcomes, clinical pregnancy rate, miscarriage rate, multiple pregnancy rate, ovarian hyperstimulation rate.

Results: 200 patients were included (100 in each group). No statistical difference between both groups regarding the basal criteria. The ovulation rate in the letrozole cabergoline (group1) was 75% versus 60% in the letrozole (group 2) with *p-value* 0.023* .Additionally, number of dominant follicle ≥17mm was significantly more in the letrozole cabergoline group than in other letrozole group with (*p value* 0.00**). There was noticed also that stimulation days are less in letrozle cabergoline group than letrozole only group but not reach significance. Patients in letrozole cabergoline group had a higher clinical pregnancy rate reaching 27.0% versus 15.0 % in patients of the letrozole group (*p-value* 0.037*) No difference between both groups as regard the miscarriage multiple gestation, ovarian hyperstimulation rate and the side effects of the study medications.

Conclusions: Higher ovulation and clinical pregnancy rate with the use of cabergoline and letrozole during ovulation induction in euprolactinemic infertile pcos than use letrozole alone.

Key Words: Cabergoline, euprolactinaemia, letrozole, pco.

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INTRODUCTION

polycystic ovary syndrome (PCOS) is a common reproductive endocrinological disorder causing anovulatory infertility .There will be wide spectrum of clinical findings including: hyperandrogenemia,insulin resistance , increasing luteinizing hormone (LH) secretion, menstrual irregularity, hirsutism ,anovulatory infertility[1]. According to the Rotterdam criteria ,pco is diagnosed by presence of at least two out of three features; presence of oligo- or anovulation ,evidence of clinical or biochemical hyperandrogenism and ultrasound appearance of polycystic ovaries[2]. PCOS represent 5-10% of women in reproductive age affecting their fertility and their health[3].

It was found that about 65–70% of women with PCOS having nsulin resistance with compensatory hyperinsulinemia[4]. 70–80% of them (pco with insulin resistance) are obese (BMI >30) and 20-25% are lean (BMI<18). Insulin resistance mainly related to PCOS independent of obesity,results from abnormalities of cellular mechanisms of insulin action and post insulin receptor function. The hyperinsulinemia seems to be an important factor maintaining hyperandrogenemia with its negative effects on both reproductive and metabolic health[5]. So correction of insulin resistance and consequently hyperandrogenemia is of great importance in treatment options of pco regarding improving reproductive &metabolic conditions[5,6].

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Different modalities for treating insulin resistance/ hyperinsulinemia including lifestyle modifications, exercise, dieting and weight loss, or administration of medications e.g metformin. weight reduction by using of metformin plus lifestyle modification (exercise and diet) has been approved their efficacy in reducution of hyperandrogenism,increasing ovulation and conception rate, together with improving the metabolic condition as documented by many studies[7,8].

Cabergoline is a potent long-acting dopamine agonist with high binding affinity and specificity for D2 receptors of dopamine. It is more effective, tolerated and four times more potent than bromocriptine[9]. Falaschi *et al*., 1986; Prelevic *et al*., 1987approved presence of dopaminergic inhibitory control on gonadotrophin secretion,and suggested that a reduction of this inhibitory effect might cause abnormal PRL and LH release, as found in PCOS patient[10,11]. Different studies concluded that the administration of cabergoline can improve insulin resistance and consequently normalize androgen levels in pco anovulatory women and thus improving their menstrual irregularity[12]. In addition,cabergoline as dopamine agonist play an important role in decreasing high prolactin secretion[13] that was present in about 30–40% of PCO women[14]. So dopamine agonists can induce ovulation in PCOS anovulatory women with increased prolactin through reduction of its serum level in patient with high level ,moreover they may induce ovulation in those with normal prolactin level[15]. This could be attributed to reduction of an occult hyperprolactinemia (a transient rise in plasma prolactin (PRL) concentrations could be noticed during the late follicular and luteal phases of both natural and stimulated cycles) in PCOS patients[16].

Other studies documented that cabergoline in PCOS patients produce better ovarian response, reduced the risk of ovarian hyperstimulation syndrome (OHSS), and decreased serum prolactin concentration with no increase in pregnancy rate[17]. Therefore, this present study was designed to detect effect of using cabergoline in patient with anovulatory pco with normal prolactin level regarding ovarian response (ovulation rate, pregnancy rate) as primary outcome during aromatase inhibitor (letrozole) stimulation protocol in pco.

PATIENT & METHODS

Type & place of study

This is randomized, prospective,controlled study was conducted in outpatient clinic of obstetric &gynaecology department of zagazig University& private practice clinic during the period from April 2018 to April 2019 , all participants gave their written informed consent before their inclusion in the study.

Patients

Study included (200) infertile women with anovulatory PCOS,based on the Rotterdam criteria (2003 ESHRE/ ASRM consensus)[18], whereby the diagnosis of PCOS requires the presence of two of three criteria, i.e., oligomenorrhea and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and/or polycystic ovaries on ultrasound.other inclusion criteria were: age of women between 18 and 35 years at the time of study; with primary or secondery infertility for period up to 3 years; and basal serum follicle stimulating hormone level (FSH) <10 mIU/mL in the early follicular phase; normal seum prolactin level < 24 ng/dl, with no galactorrhea.

All women had bilateral tubal patency detected by hysterosalpingography or laparoscopy and with normal semen analysis for their partener according to the modified WHO criteria 2010[19]; but patients with history of laparoscopic ovarian drilling or ovarian cystectomy; hyperprolactinemia,thyroid disorders, uterine pathology such as leiomyoma, adenomyosis,or congenital uterine malformation,patients with male factor or hypersensitivity or contraindications to letrozole &or cabergoline are excluded.

Randomization

Patients were randomly allocated into two groups using a computer-generated sequence and the randomization list was held in a secure box The randomization was done by computer-generated random table. women who gave their informed consent were randomized to either group 1: (letrozole + cabergoline) or group 2: (letrozole alone). Allocation was done using odds numbered for group I.

Closed opaque envelopes. Each envelope was labeled with a serial number and had a card with written intervention. All participants were assigned to their groups according to their number and what written in card ,group (I) letrozole plus cabergoline group, (100) patient received Letrozole (2 Tablets) 5mg oral daily from cycle day 3 of spontaneous or progestin induced cycle for 5days plus cabergoline (Dostinex® tablet), 0.25 mg once weekly for 4 week starting from cycle day 3 with letrozole.

Group (II) receive letrozole 5mg(2tablet)oral only from cycle day 3 of spontaneous or progestin induced cycle for 5days.

Stimulation protocol

Group I (letrozole cabergoline gp): patients received letrozole(Femara 2.5 mg tablet; Novartis Pharma Services, Switzerland) 5 mg/day on two divided doses each 2.5mg starting from cycle day 3 for 5 days plus cabergoline (Dostinex® tablet) 0.25mg ,half tablet once weekly for 4 week starting from cycle day 3 with letrozole.

Group II (letrozole GP): patients received letrozole only with the same dose and duration as 1st group .For all participants in both groups on cycle day 3, proper history taking with collected information regarding ; age , parity, BMI, duration of infertility and the results of basal investigations including uls, FSH, LH and prolactin.

On cycle day 10 ultrasound folliculometry was done for all patients in both groups ,(by the same sonographer, who was blinded by their intervention group, using a SonoacenX4 machine (Medison, Korea) with transvaginal probe (4–8 MHz frequency)), for evaluation of number, size of ovarian follicles in each ovary,endometrial thickness.

Frequency of visit was tailored according to size of follicle till dominance was confirmed or excluded when the leading follicle size≥ 18 mm in diameter, 10,000 IU of highly purified hCG (Choriomo, IBSA, Lugano, Switzerland was given intramuscular injection, timed coitus is asked within the following 36 hours.

2 weeks after the end of treatment . Midluteal progesterone (one week after presumed ovulation or one week after the last observation) was assayed. Only one complete treatment cycle was offered to each women of both groups.

Outcome measures

The primary outcome was the rate of ovulation in both groups. no of mature follicles,stimulation days.

The secondary outcomes included clinical pregnancy rate (number of patient with intra uterine gestational sac with fetal pulsation detected by ultrasound), miscarriage rate (the number of cases with pregnancy loss within 10 weeks of gestation), the multiple pregnancy rate.

RESULTS

206 Pco patients were recruited in this study, four patients excluded from the start; one refused to participate&3 not met the inclusion criteria.The remaining (202) patients were randomly allocated into two groups (101) in each group, however, one case was lost (did not attend) for follow up letrozole cabergoline group and one case not responding and need adding gonadotropin ingection from letrozole group). So the final analysis on 200 patient,100 in each group.

Both groups were comparable to each other regarding their demographic characters with no significant difference (Table 1).

Table 1: Basic demographic and clinical data distribution between studied groups

			Group 1	Group 2	t/ X^2	*P*
Age (years)			26.72±6.0	26.86±3.77	1.954	0.052
BMI			26.24±2.38	26.26±2.42	0.178	0.942
Duration of infertility(years)			2.38±0.54	2.42±0.54	1.312	0.125
PRL			11.77±3.72	11.44±2.98	1.105	0.255
TSH			2.22±0.62	2.17±0.61	1.621	0.0841
Type of infertility	Primary	N%	42 (42.0%)	53 (53.0%)	2.42	0.11
	Secondary	N%	58 (58.0%)	47 (47.0%)		
Total		N	100	100		

There was no significant difference or association regard basic demographic and clinical data.

But there was statistically significant difference regarding both ovulation and number of largest follicle follicle ≥17mm (Table 2)

Ovulation was achieved in75 patients about ,75.0% ovulation rate (group1, received cabergoline –letrozole) ,while in (group 2 received letrozole only) it is achieved in 60 patients (60.0% ovulation rate) with *p-value* 0.023*).

Inaddition, the number of follicle ≥17mm was significantly more in the letrozole cabergoline group than in other letrozole group with (*p value* 0.00**) (Table 2).

There was noticed also that stimulation days are less in letrozle cabergoline group than letrozole only group but not reach significance (Table 2).

Table2: Stimulation character in both groups.

		Group 1	Group 2	t/ Mann Whitney/ X^2	*P*
Stim days		12.57±1.33	14.07±1.51	1.412	0.097
No of large follicle ≥17mm		3.0 (2-3)	1.0 (1-2)	Z=8.621	0.00**
Endo thickness		9.46±1.41	9.01±1.19	1.422	0.1013
Ovulation rate	N	75 (75.0%)	60 (60.0%)	5.12	0.023*

Stimulation days shorter but not significantly in 1st group, No of large follicle and ovulation rate was sig higher among 1st group

Clinical pregnancy; defined as sonographically visualized intra-uterine gestational sac with pulsating fetal pole was achieved in 27 cases with (27.0%) % among letrozole cabergoline group and only in 15 (15.0%) cases in letrozole group with (*p- value* 0.037*) (Table 3).

Table 3: Response of stimulation

	Group 1 N (%)	Group 2 N (%)	t/ Mann Whitney/ X2	*P*
Chemical pregnancy	5 (5.0%)	7 (7%)	35	55
Clinical pregnancy	27 (27.0%)	15 (15.0%)	4.31	0.037*
Twin pregnancy	8 (8.0%)	5 (5.0%)	0.74	0.38
miscarraige	3 (11.1%)	2 (13.3%)	0.04	0.83

This table show that there is statistically significant difference in clinical pregnancy rate between both groups in favour of group 1.

DISCUSSION

There is no fixed protocol for induction of ovulation in women with PCOS, it can be achieved, either medically or surgically. but to use the least invasive method first is the logical approach.It was found that 30–40% of PCOS women with hyperprolactinaemia[8] so dopamine agonists can be helpful in induction of ovulation in these patients through reduction of the serum prolactin level.

Moreover, it was found that it improve and induce ovulation in pco infertile anovulatory patients with normal prolactin level[9]. This effect could be related to reduction of an occult hyperprolactinemia in PCOS patients[10].

Parsanezhad *et al*. (2002) followed prolactin level in euprolactinemic patients and foud there is diurnal variation of prolactin secretion that leads to Occult hyperprolactinemia in some patients[20].

Cabergoline is a dopamine agonist, with higher affinity to dopamine D2 receptors different studies showed improvement of ovulation rate and pregnancy rate with its use in pco patient[21].

This randomized study was conducted in infertility clinic of zagazig university&private Clinic of our hospital during the study period .We included PCOS women with normal prolactin level < 24 ng/dl, no galactorrhea and diagnosed as PCOS according to Rotterdam criteria[4].

In this study we try to detect value of adding cabergoline with letrozole for induction of ovulation in PCOS patients although normal prolactin.

In this study there was statistically significant difference regarding both ovulation rate and number of largest follicle follicle ≥17mm (Table 2).

Ovulation rate (group1, cabergoline –letrozole) 75 % in comparison to 60.0% (ovulation rate with *p-value* 0.023*) in group 2 received letrozole only, Inaddition, the number of follicle ≥17mm was significantly more in the letrozole cabergoline group than in other letrozole group with (*p value* 0.00**) (Table 2).

There was noticed also that stimulation days are less in letrozle cabergoline group than letrozole only group but not reach significance (Table 2),

Also clinical pregnancy rate was higher (27.0%) among letrozole cabergoline group and only in (15.0%) in letrozole group with (*p- value* 0.037*) (Table 3).

This was consistent with study done in Assuit university by Zahran *et al* (2017) who use clomid plus cabergoline in pcos euprolactinaemic patient and found ovulation rate was 76.7% and the pregnancy rate was 31.7%[22].

Another study by Suha witwit in Iraq consistent w our results found that improvement in both ovulation rate and pregnancy rate in the cabergoline group to be 86% & 36 % respectively versus 64% & 14% in the clomiphene group ($p = 0.001$)[23].

On the other side Kubota *et al*. (1992) reported a lower ovulation rate of 57.3% and pregnancy rate of 26.7% when used clomiphene citrate and bromocriptine not cabergoline in euprolactinemic infertile women &clomid resistant[24].

This difference could be explained by different pharmacological effect of cabergoline and bromocriptine in addition patients are not PCOS.

Going with our current study, Xue *et al*. who reported that there is value of bromocriptine and CC in infertile patients with the normal prolactin level but with galactorrhea in pregnancy rate and lowering miscarriage[25].

Another study showed that cabergoline can enhance endometrial perfusion and regulate menstrual cycle in PCOS patients which indirectly increases endometrial receptivity and thus improve pregnancy outcome[26].

This effect of cabergoline is explained by its ability to inhibit the vascular endothelial growth factor (VEGF) secretion in luteinized granulosa cells[27]. Inaddition to its inhibitory effect on LH and androgen secretion, with improving insulin resistance helping in good ovulation response 75%[28].

On contrary, Tripathy *et al* ,found that there is no value of adding bro mocriptine to clomiphene citrate for stimulation of ovulation PCOS women with euprolactinemia, ovulation rate was 69% with CC, while 76% with bromocriptine and CC, and bromocriptine has a more adverse side effect[29].

Also ,Parsanezhad *et al*.declared that no significant differences in the ovulation and pregnancy rates whith adding bromocriptine to CC in CC resistant euprolactinemic PCOS patients and the only benefit of bromo criptine therapy inCC-resistantPCOSpatientswas to normalize the level of the serum prolactin. But this study differ from current study in studied group are clomiphene resistant pcos female.

CONFLICT OF INTERESTS

There are no conflicts of interest.

REFERENCE

1. Boomsma CM, Eijkemans MJC, Hughes EG, Visser GHA, Fauser BCJM, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Human Reprod Update 2006; 12: 673-83

2. ESHRE REA-SPCWG, Revised 2003 consensus on diagnostic criteria and longterm health risks related to polycystic ovary syndrome (PCOS), Hum. Reprod. 2004;19: 41–7

3. Asunción M, Calvo RM, San Millán JL, Sancho JAvila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab. 2000; 85: 2434-8.

4. DeUgarte CM, Barolucci AA, Azziz R. Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. Fertil Steril. 2005; 83:1454–60.

5. Ciaraldi TP, el-Roeiy A, Madar Z, Reichart D, Olefsky JM, Yen SS. Cellular mechanisms of insulin resistance in polycystic ovarian syndrome. J Clin Endocrinol Metab. 1992; 75:577–83.

6. Dunaif A, Xia J, Book CB, Schenker E, Tang Z. Excessive insulin receptor serine phosphorylation in cultured fibroblasts and in skeletal muscle. A potential mechanism for insulin resistance in the polycystic ovary syndrome. J Clin Invest. 1995; 96:801–10.

7. Norman RJ, Davies MJ, Lord J, Moran LJ. The life style modification in polycystic ovary syndrome. Trends Endocrinol Metab. 2002; 13:251–7. [PubMed: 12128286]

8. Hoeger KM. Exercise therapy in polycystic ovary syndrome. Semin Reprod Med. 2008; 26:93–100.

9. Essah PA, Wickham EP, Nestler JE. The metabolic syndrome in polycystic ovary syndrome. Clin Obstet Gynecol. 2007; 50:205–25.

10. Falaschi P, Frajese G, Rocco A, Toscano V, Sciarra F. Polycystic ovary syndrome and hyperprolactinemia. J Steroid Biochem 1977; 8: 13.

11. Prelevic GM, Wurzburger MI, Peric LJA. Acute effects of L-dopa and bromocriptine on serum PRL, LH and FSH levels in patients with hyperprolactinemic and normoprolactinemicpolycystic ovary sydrome. J Endocrinol Invest 1987;10,389-95.

12. Azam Ghaneei., Akram Jowkar, Mohammad Reza Hasani Ghavam Mohammad Ebrahim Ghaneei. Cabergoline plus metformin therapy effects on menstrual irregularity and androgen system in polycystic ovary syndrome women with hyperprolactinemia. Iran J Reprod Med 2015; 13(2),93-100.

13. Dos Santos Silva CM, Barbosa FR, Lima GA, BMI and Metabolic Profile in Patients with Prolactinoma before and After Treatment with Dopamine Agonists, Obesity (Silver Spring) .2011 ;19, 800–5.

14. V. Melgar, E. Espinosa, E. Sosa, *et al*., Current diagnosis and treatment of hyperprolactinemia, Rev. Med. Inst. Mex. Seguro Soc. 2016;54 (1), 111–21.

15. B. Corenblum, P.J. Taylor, A rational for the use of bromocriptine in patients with amenorrhea and normoprolactinemia, Fertil. Steril.1980; 34 ,239–41.

16. F. Peilon, M. Vincens, F. Ceselin, R. Doumit, I. Mouszowics, Exaggerated-prolactin response to thyrotropin-releasing hormone in women with anovulatory cycles: Possible role of endogenous estrogens and effect of bromocriptine, Fertil. Steril. 1982;37,530–35.

17. Papaleo E, Doldi N, De Santis L, Marelli G, Marsiglio E, Rofena S, *et al*. Cabergoline influences ovarian stimulation in hyperprolactinaemic patients withpolycystic ovary syndrome. Hum Reprod 2001; 16,2263-66

18. ESHRE REA-SPCWG, Revised 2003 consensus on diagnostic criteria and longterm health risks related to polycystic ovary syndrome (PCOS), Hum. Reprod.2004,19,41-7.

19. T.G. Cooper, E. Noonan, S. Von Eckardstein, *et al*., World Health Organization reference values for human semen characteristics, Hum. Reprod Update 2010,16,3,231-45.

20. M.E. Parsanezhad, S. Alborzi, B.N. Jahromi, A prospective, double-blind, randomized, placebo-controlled clinical trial of bromocriptine in clomiphene-resistant patients with polycystic ovary syndrome and normal prolactin level, Int. J. Fertil. Womens Med. 47 (6) (2002) 272–277. [19] E. Papaleo, N. Doldi, L. De Santis, G. Marelli, E. Marsiglio, S. Rofena, *et al*.,

21. L.B. Nachtigall, Cabergoline for hyperprolactinemia: getting to the heart of it, Endocrine 57 (1) (2017) 3–5.

22. Kamal M. Zahrana, Waleed A. Mostafab, Ahmed M. Abbasa, Mansour A. Khalifaa, Gamal H. Sayed, Clomiphene citrate plus cabergoline versus clomiphene citrate for induction of ovulation in infertile euprolactinemic patients with polycystic ovary syndrome: A randomized clinical trial , Middle East Fertility Society Journal 23(2018)173-177

23. Suha Witwit ,Improving pregnancy rate in infertile patients with polycystic ovarian syndrome receiving clomiphene citrate and cabergoline in euprolactinomic women in single cycle treatmenGinekologia ,,,Polska 2023, vol. 94, no. 6, 456–462

24. T. Kubota, S. Kamada, T. Aso, Combined therapy with bromocriptine and clomiphene citrate for patients with normoprolactinemic amenorrhea, Int. J. Fertil. 37 (1992) 277–282.

25. T. Xue, S. Wei Li, Y. Wang, Effectiveness of bromocriptine monotherapy or combination treatment with clomiphene for infertility in women with galactorrhea and normal prolactin: a systematic review and meta-analysis, Curr. Ther. Res. Clin. Exp. 71 (2010) 199–210.

26. H. Ferrero, C.M. Garcia-Pascual, N. Pellicer, *et al*., Dopamine agonist inhibits vascular endothelial growth factor protein production and secretion in granulosa cells, Reprod. Biol. Endocrinol. 13 (2015) 104.

27. R. Mohammadbygi, S.R. Yousefi, S. Shahghaybi, S. Zandi, K. Sharifi, F. Gharibi, Effects of cabergoline administration on uterine perfusion in women with polycystic ovary syndrome, Pak. J. Med. Sci. 29 (4) (2013) 919–922

28. H. Chen, J. Fu, W. Huang, Dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia andrecurrent miscarriage history, Cochrane Database Syst. Rev. 7 (2016) CD008883. [14] T.G. Cooper, E. Noonan, S. Von Eckardstein, *et al*., World Health Organizatio

29. S. Tripathy, S. Mohapatra, M. Muthulakshmi, A. Chandrasekhar, Induction of ovulation with clomiphene citrate versus clomiphene with bromocriptine in PCOSpatients.