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Original Article

Adding Cabergoline to Clomiphene Citrate for treatment of unexplained infertility: does it really add?

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Abstract

Keyword:
Unexplained infertility, Clomiphene citrate, Cabergoline, Ovulation induction

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Background:
Unexplained infertility is the absence of identifiable cause for infertility and the female's inability to get pregnant after at least 12 months of unprotected sexual intercourse for whom all the standard evaluations are normal.

Objective: Our study aims to assess the effectiveness of adding Cabergoline to Clomiphene citrate in management of women complaining of unexplained infertility.

Materials & Methods:
120 Patients diagnosed with unexplained infertility were randomized to Clomiphene citrate plus cabergoline or Clomiphene citrate alone. All Patients were followed up for three cycles by transvaginal ultrasound folliculometry to document the number and size of mature graffian follicles and ovulation. The primary outcome of the study was the number and size of mature follicles. The secondary outcomes included the occurrence of ovulation, pregnancy rate, abortion rate, endometrial thickness, and the rate of adverse effects of the study medications.

Results:
There is a statistically significant difference regarding to the number ($P<0.001$), size of follicles ($P<0.001$), occurrence of ovulation ($P=0.04$, 0.006, 0.016) and endometrial thickness ($P=0.000$) between the two groups in the favor of adding Cabergoline to Clomiphene citrate.

Conclusion:
Adding Cabergoline to Clomiphene citrate in induction of ovulation in euprolactinemic infertile women with unexplained infertility results in high ovulation rate, better endometrial thickness and high pregnancy rate compared to use of Clomiphene citrate alone.

INTRODUCTION:

Unexplained infertility may be diagnosed in as many as 30% of infertile couples.[1] Unexplained infertility is the absence of identifiable cause for infertility.[2] The diagnosis of unexplained infertility implies normal semen analysis, ovulatory function, a normal uterine cavity, and at minimal unilateral tubal patency.[3] Clomiphene citrate (C.C) is a nonsteroidal triphenylethylene derivative that acts as a selective estrogen receptor modulator (SERM).[4] It is used for induction of ovulation in most patients with a success rate of 70-80% of well selected women.[5] Cabergoline is an ergot-derived dopamine agonist with a long half-life and it is an effective prolactin suppressor. So, the question is: What is the hypothesis of adding cabergoline as an adjuvant to Clomiphene citrate for treatment of Unexplained infertility?? (1) About 30% of asymptomatic women with otherwise unexplained subfertility have mild endometriosis if laparoscopy is undertaken.[6] In 2009 study was done to evaluate the anti-angiogenic properties of Cabergoline on growth of established endometriosis lesions. The conclusion was that Cabergoline treatment in experimental endometriosis has an anti-angiogenic effect acting through VEGFR-2 activation which suggests the testing of dopamine agonists as a novel therapeutic approach to peritoneal endometriosis in humans.[7] Also another study was done on angiogenesis and antiangiogenic treatment in endometriosis and the conclusion was that anti-angiogenic compounds hold great promise for the future treatment of endometriosis.[8] (2) In cases of macroprolactinemia; (Asymptomatic hyperprolactinemia) Macromolecular form of prolactin is generally associated with asymptomatic hyperprolactinemia. It could have clinically insignificant laboratory abnormality.[9] Olukoga and Kane determined in patients with macroprolactinemia that dopamine agonists decreased macroprolactin levels and improved hyperprolactinemic symptoms, and cessation of the therapy with dopamine agonists resulted in rebound hyperprolactinemia in all patients.[10] (3) Cabergoline can increase uterine blood flow, androgen decreases markedly during Cabergoline treatment.[11](4) Whereas mild OHSS (moderate ovarian enlargement) is relatively common, severe OHSS is rarely observed with OHSS.[12] This syndrome has been managed expectantly by Dopamine agonist Cabergoline which reduce severity of ovarian hyperstimulation syndrome.[13] So, we hypothesized that adding Cabergoline to Clomiphene citrate during ovulation induction in female patients

with unexplained infertility will improve number & size of mature follicles , ovulation rate.

PATIENT AND METHODS:

This is a randomized controlled prospective study, conducted in Assiut University Women's Health Hospital, Egypt.

Reviewing the proposal was carried out and approved before starting data collection via the Ethical review Committee of Assiut Faculty of Medicine, privacy, and confidentiality of all the data were assured and the aim of the study was explained to each participant before starting the treatment. Informed written consent was obtained from those who welcome to participate in the study.

120 patients were recruited for this study among patients attended outpatient infertility clinic at Assiut University Women's Health Hospital suffering from 1ry or 2ry infertility and diagnosed to have unexplained infertility. They were randomized into two groups : Group (A) Consisted of 60 patients who received a dose of Clomiphene citrate 100 mg tablet from the second day of menses to the sixth day (Clomid by tradename, produced by Sanofi Aventis, Global Napi pharmaceuticals under license of Sanofi Aventis - France) and cabergoline 0.25 mg (Cabergamoun by tradename was used, produced by Amoun pharmaceuticals, license No. 26671-2010) half tablet every 3 days for 9 days (one package) and Control Group (B) Consisted of 60 patients who received a dose of Clomiphene citrate 100 mg tablet from the second day to the sixth day of menses only. The randomization was done by computer-generated random table. Allocation concealment was done using serially numbered closed opaque envelopes. Each envelope was labeled with a serial number and had a card noting the intervention type. Allocation was never changed after opening the closed envelopes. All the following were done to all study subjects: Full history taking, general, abdominal, gynecological and breast examination, hormonal analysis in the form of basal FSH (normal: 3-10 mIU/ml), LH (normal: less than 7 mIU/ml), and prolactin (2 to 29 ng/ml) on 3rd day of the cycle, human chorionic gonadotropin (HCG) was used as an ovulation trigger in women. In such

cases, exogenous HCG in a dose of 5000 IU is given as a single intramuscular dose when the dominant follicle reaches 18-20mm.[14] In cycle day 13, all patients were evaluated by ultrasound examination through the same sonographer (Level II experience), who was blinded by their intervention group, using a SonoAce X8 machine (Medison, Korea) with transvaginal probe (4–8 MHz frequency). Transvaginal sonography (TVS) was done for evaluation of number, size of ovarian follicles at each side. All patients were followed up for 3 consecutive cycles. Patients were followed up for three cycles by transvaginal ultrasound folliculometry to document the size (in mm) of mature graffian follicle and ovulation.

Statistical analysis and Sample size calculation:

All data were analyzed using SPSS software Chicago, IL, USA, version 21. Testing the normality of data distribution was done by the Shapiro-Wilk test. Qualitative data were expressed as frequency and percentage. Chi-square test was used to examine the relation between qualitative variables. Quantitative data were presented in terms of, mean, standard deviation as they were normally distributed. For quantitative data, comparison between two groups was done using Independent T-test test. Level of significance ‘‘P” value was evaluated, where P value < .05 is considered of significant value.

Sample size calculation was carried out using G*Power 3 software. A calculated sample of 120 patients with unexplained infertility (60 in each arm – Clomiphene citrate and cabergoline Vs Clomiphene citrate alone) will needed to detect an effect size of 0.3 in the percentage of those with successive ovulation, with an error probability of 0.05 and 80% power.[15]

RESULTS:

One-hundred fifty-three patients were approached to participate in this study. Twelve women were excluded as they did not meet the inclusion criteria. Moreover, four women refused to participate in the study. The remaining 137 patients were randomly assigned to the two groups. Nine patients in group A and eight patients in group B did not complete the scheduled course of treatment or did not attend the follow up visits so they were excluded from the final analysis (Fig. 1, the study

flowchart). There were no statistically significant difference regarding to the socio-demographic or obstetric data (Table 1), semen parameters or basal hormonal profile (table 2) between the two groups. There were a statistically significant difference regarding to the number, size of follicles, occurrence of ovulation (Table 3), endometrial thickness (Table 4) between the two groups in the favor of group A. despite being not statistically significant, women in the cabergolin group reported high pregnancy rate as compared to the control group, 13 (21.7%) VS. 7 (11.7) %. There were no statistically significant difference between the two groups regarding to the occurrence of pregnancy (Table 5), the side effects of the drug (Reported only headache and some GIT upset in 4 cases in group A and two cases of GIT upset in group B), the number of fetuses (Table 5) or the mode of delivery (Table 5) between the two groups.

DISCUSSION:

To the best of our knowledge, this is the first study that addresses the effect of adding Cabergoline to induction of ovulation agents in management of patients with unexplained infertility. In our current study, Cabergoline was well tolerated by all the patients and no adverse effects were observed. The results of this study are encouraging. Furthermore, almost no manifestations of OHSS were reported. There are many randomized placebo-controlled trials published to identify the effect of dopamine agonist treatment on ovulation and pregnancy outcome in cases with PCOS, but their results are conflicting. Some studies reported significant improvements in ovulation and pregnancy rate with Clomiphene citrate after taking dopamine agonists in women with PCOS and normal prolactin levels. Enrico P. et al; 2001[16]: is a study that evaluated retrospectively the clinical effect of Cabergoline, a strong Dopamine agonist and inhibitor of PRL secretion, on ovarian response (ovarian size, number of follicles developed, peak E2 at HCG administration) during recombinant FSH (rFSH) stimulation protocols in such patients and that supported the evidence of dopaminergic component in the control of LH release in PCOS patients, and suggest that a pre-treatment with Cabergoline reduces ovarian response to rFSH without interfering with pregnancy rate or increasing the possibility of multiple pregnancy. Although these data are not statistically

significant, this approach should be investigated as a potentially important option for limiting the risk of OHSS in such patients. Another study was a randomized controlled prospective study and was conducted in Assiut University Women's Health Hospital on patients with (PCOS). Study group received a dose of Clomiphene citrate 100 mg tablet from the second day of menses to the sixth day and Cabergoline 0.25 mg (half tablet) every 3 days for 9 days (one package). The control group received a dose of Clomiphene citrate alone tablets with same dose and duration. That study has found out that there was a statistically significant difference in size and number of follicles between the two groups in the favor of Clomiphene and Cabergoline group. There was also a statistically significant difference in outcome of ovulation induction between the two groups in the favor of Clomiphene and Cabergoline group. Another statistically significant difference was found between study and control groups in the occurrence of pregnancy in the favor of the study group. There is no statistically significant difference in abortion or multifetal pregnancy rates between study groups.[17] In our current study all unexplained infertility patients fulfilled the criteria of normal semen parameters (male factor), HSG and baseline hormonal profile. (Female factor)[1] There was no statistically significant difference regarding to the age, BMI, duration of infertility, the semen parameters or the baseline hormonal profile between the two groups. The cumulative ovulation rate in our study group was 93.3% and the pregnancy rate was 21.7%. Kubota T. et al. 1992[18] reported a lower ovulation rate of 57.3% and pregnancy rate of 26.7% in their study using combined Clomiphene citrate and Bromocriptine in euprolactinemic infertile women . They did not include PCOS patients beside the different pharmacological effect of Cabergoline and this could explain the difference in results. Zahran K. et al ., 2018[17] reported a lower ovulation rate of 76.7% and higher pregnancy rate of 31.7% in their study using combined Clomiphene citrate and Cabergoline in PCO infertile women. We are dealing with unexplained infertility patients not PCO so the quality of patients could explain the difference in results. There was a statistically significant difference regarding to the endometrial thickness between the two groups in the favor of Clomiphene and Cabergoline group and this could be explained by the role of Cabergoline in improving the uterine perfusion. The main item in the strength of our current study is the randomized design. We were able to recruit our calculated

sample size for achieving adequate power to detect a clinically significant difference in our primary outcome. Additionally, the study was conducted at the same clinic, with a single sonographer to avoid any inter-assessor variation in ultrasound evaluation. The study had its some limitations; We didn't use the live birth rate in the study outcomes. However, we suggest that clinical pregnancy rate is relevant and important and is commonly used in many studies. All the patients included in the study were followed up till three months of induction of ovulation or till pregnancy occurred and the fate of this pregnancy was also followed up.
The main Conclusion of the study is, Adding Cabergoline to Clomiphene citrate in induction of ovulation in euprolactinemic infertile women with unexplained infertility results in high ovulation rate, better endometrial thickness and high pregnancy rate compared to use of Clomiphene citrate alone. Future studies are needed to address the effects of adding Cabergoline to Clomiphene citrate on the endometrial receptivity and Doppler indices in the uterine artery in unexplained infertility patients.

Ethics approval and consent to participate:

Reviewing the proposal was carried out and approved via the Ethical review Committee of Assiut Faculty of Medicine.

Consent for publication: Not applicable.

Competing interests:
The authors declare that they have no competing interests.

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No grant was accepted for this Study by any foundation.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
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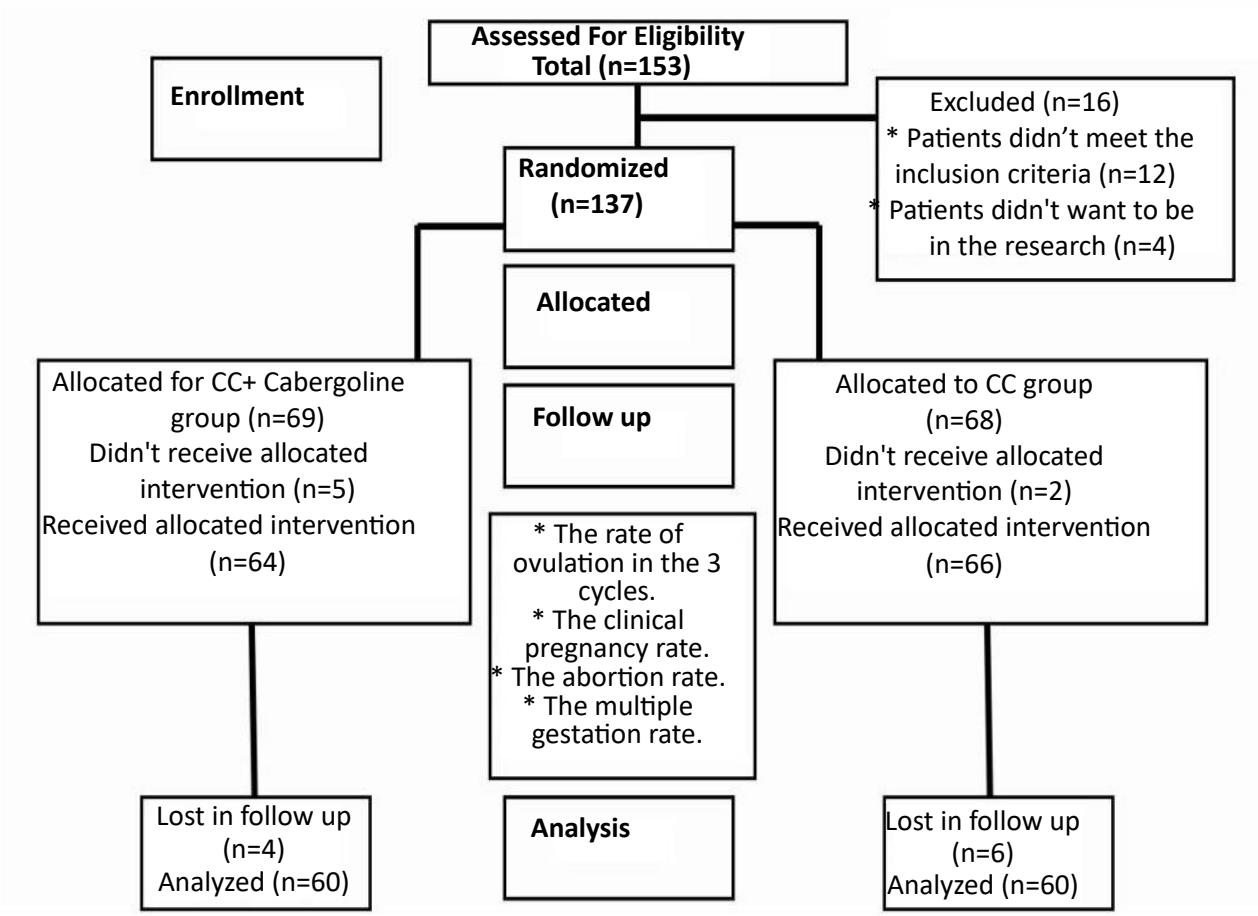
Flow chart


Enrollment
Assessed For Eligibility
Total (n=153)
Excluded (n=16)
* Patients didn't meet the inclusion criteria (n=12)
* Patients didn't want to be in the research (n=4)
Randomized
(n=137)
Allocated
Follow up
Allocated for CC+ Cabergoline group (n=69)
Didn't receive allocated intervention (n=5)
Received allocated intervention (n=64)
Allocated to CC group (n=68)
Didn't receive allocated intervention (n=2)
Received allocated intervention (n=66)
* The rate of ovulation in the 3 cycles.
* The clinical pregnancy rate.
* The abortion rate.
* The multiple gestation rate.
Lost in follow up (n=4)
Analyzed (n=60)
Analysis
Lost in follow up (n=6)
Analyzed (n=60)

(Table 1): Socio-demographic and obstetrical data of the studied groups.

	Group A (n= 60)		Group B (n= 60)		P-value
	No.	%	No.	%	
Age: (years)					
Mean ± SD	25.87 ± 5.35		27.20 ± 4.32		0.136
BMI:					
Mean ± SD	24.53 ± 3.35		25.58 ± 3.78		0.110
Occupation:					
Housewife	56	93.3%	56	93.3%	1.000
Employee	4	6.7%	4	6.7%	
Husbands occupation:					
Employee	14	23.3%	10	16.7%	
Farmer	18	30.0%	18	30.0%	0.627
Worker	28	46.7%	32	53.3%	
Gravidity:					
0	30	50.0%	30	50.0%	
1- 2	18	30.0%	16	26.7%	0.873
3 or more	12	20.0%	14	23.3%	
Parity:					
No	32	53.3%	40	66.7%	
1- 2	18	30.0%	14	23.3%	0.303
3 or more	10	16.7%	6	10.0%	
Menstrual regularity:					
Regular	60	100.0%	58	96.7%	0.496
Irregular	0	0.0%	2	3.3%	

SD: standard deviation

(Table 2): Semen parameters According to WHO 2010 and Baseline hormonal profile of the studied groups.

	Group A (n= 60)	Group B (n= 60)	P-value
	Mean ± SD	Mean ± SD	
Semen parameters			
Concentration (mill/ml)	**28.86 ± 22.79**	**30.06 ± 16.56**	**0.132**
Motility A+B	**39.22 ± 8.82**	**40.75 ±**	**0.29**
Normal Forms	**8.78 ± 3.18**	**9.60 ± 3.42**	**0.178**
Hormonal profile			
FSH	**5.05 ± 0.90**	**5.02 ± 1.45**	**0.892**
LH	**3.79 ± 0.85**	**3.68 ± 0.85**	**0.471**
PRL	**13.01 ± 2.48**	**12.96 ± 3.31**	**0.931**
TSH	**2.27 ± 0.65**	**2.15 ± 0.77**	**0.366**

(Table 3): Number of follicles, Size of follicles and Ovulation of the studied groups.

	Group A (n= 60)	Group B (n= 60)	P-value
	Mean ± SD	Mean ± SD	
No. of follicles			
1st cycle	**3.12 ± 1.19**	**1.18 ± 0.43**	**0.000***
2nd cycle	**2.91 ± 1.33**	**1.21 ± 0.45**	**0.000***
3rd cycle	**2.85 ± 1.50**	**1.11 ± 0.31**	**0.000***
Size of follicle			
1st cycle	**22.43 ± 2.12**	**16.07 ± 1.82**	**0.000***
2nd cycle	**22.31 ± 1.75**	**17.12 ± 1.70**	**0.000***
3rd cycle	**21.97 ± 2.91**	**16.68 ± 2.31**	**0.000***

Ovulation	N.	%	N.	%	
1st cycle:					
Yes	42	70.0%	31	51.7%	0.040*
No	18	30.0%	29	48.3%	
2nd cycle:					
Yes	40	75.5%	29	50.0%	0.006*
No	13	24.5%	29	50.0%	
3rd cycle:					
Yes	34	72.3%	28	49.1%	0.016*
No	13	27.7%	29	50.9%	

(*) Statistically significant difference

(Table 4): Endometrial thickness of the studied groups.

Endometrial thickness	Group A (n= 60)	Group B (n= 60)	P-value
	Mean ± SD	Mean ± SD	
1st cycle	10.10 ± 1.07	7.52 ± 1.02	0.000*
2nd cycle	9.98 ± 0.91	7.93 ± 1.02	0.000*
3rd cycle	9.94 ± 0.96	7.91 ± 1.24	0.000*

(*) Statistically significant difference

(Table 5): Obstetric Outcomes of the studied groups.

Outcome	Group A (n= 60)		Group B (n= 60)		P-value
	No.	%	No.	%	
Pregnancy:					**0.142**
Pregnant	**13**	**21.7%**	**7**	**11.7%**	
Not pregnant	**47**	**78.3%**	**53**	**88.3%**	
Pregnancy outcome:					**0.896**
Full-term	**10**	**76.9%**	**5**	**71.4%**	
Pre-term	**1**	**7.7%**	**1**	**14.3%**	
Miscarriage	**2**	**15.4%**	**1**	**14.3%**	
Number of fetuses:					**0.452**
Single	**12**	**92.3%**	**7**	**100%**	
Twins	**1**	**7.7%**	**0**	**0.0%**	
Mode of delivery:					**0.901**
V.D.	**4**	**36.4%**	**2**	**33.3%**	
C.S.	**7**	**63.6%**	**4**	**66.7%**	

(*) Statistically significant difference

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