

Investigation On The Effects Of Bromocriptine And Dexamethasone In Polycystic Ovarian Disease With Clomiphene Citrate Resistance

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Abstract

Objective: To compare the use of Bromocriptine or Dexamethasone with clomiphene in polycystic ovarian disease (PCOD) patients with clomiphene resistance.

Design: Prospective study.

Setting: Medical Science Department in Shiraz University.

Methods: A total of 133 infertile PCOD patients were seen in two years and 44 patients had clomiphene citrate resistance with the prolactin and dihydro-epiandrosterone sulfate levels were in normal range. These patients were divided into two groups of 22 each. The first group was treated with clomiphene 100 mg per day in the 5th to 9th days of cycle and with Bromocriptine 2.5 mg twice per day for three months. The second group was treated with clomiphene dosage as mentioned earlier and with dexamethasone 0.5 mg single dose nightly for three months.

Result: After treatment, regular menses resumed in 68.2% of first group and 50.0% of second group. The pregnancy rates were 40.0% and 22.7% respectively.

Conclusion: Bromocriptine showed higher rates of resumption of menses and pregnancy than dexamethasone when used in conjunction with clomiphene for polycystic ovarian disease (PCOD) patients with clomiphene resistance.

INTRODUCTION

Most couples desire pregnancy after marriage, but only 85 to 90 % of them can achieve pregnancy within 12 to 18 months of unprotected intercourse. (1) In other words, 10 to 15% of couples will remain unsuccessful in their attempts at pregnancy and are thus labeled as infertile couples. (2) There are numerous causes for infertility. Approximately 40% of infertility is due to female factors and anovulation constitutes about 40% of female infertility. (3) The polycystic ovary syndrome is one of the most common causes of anovulation infertility. (4) Clomiphene citrate is the first choice of treatment, but approximately 20% of patients with PCOD fail to ovulate despite high dose of clomiphene citrate. (5) PCOD patients who do not respond to clomiphene citrate require specialist infertility management. After 6 months of clomiphene citrate therapy and in the absence of

any other infertility factors, one of the available options is the addition of dexamethasone or bromocriptine to clomiphene citrate.

OBJECTIVE

To compare the use of bromocriptine and dexamethasone in PCOD patients with clomiphene citrate resistance.

MATERIAL AND METHOD

This was a prospective study. A total of 133 infertile PCOD patients were seen in 2 years (May 1996 to June 1998), and 44 patients who were considered to have PCOD and also clomiphene citrate failure, were selected for study in Hamzeh Clinic of Medical Science Fasa in Shiraz University. The selected patients had the following condition:

1. 2 or more of PCOD signs
2. Absence galactorrhoea
3. Normal serum prolactin
4. Normal serum DHEA-S
5. Normal coned down view (in the x-ray evaluation of sella turcica)
6. Normal H.S.G.
7. Normal spermogram
8. Failure to ovulate with high dose of clomiphene citrate

In this study patients who did not ovulate despite high dose (250mg) of clomiphene citrate in 4 months were considered as resistant. The treatment protocol was planned in two groups: First group included 22 patients treated with clomiphene citrate 100mg per day in 5th to 9th cycle days and bromocriptine 2.5 mg twice daily for 3 months. 2 patients dropped out from this group.

The second group included 22 patients treated with clomiphene citrate 100 mg per day in 5th to 9th cycle days and dexamethasone 0.5 mg single dose in bedtime for 3 months.

RESULTS

The age of patients in first group ranged from 16 to 38 years with a mean 26.9 years. The age of patients in second group ranged from 17 to 35 years with a mean 22.0 years. The duration of infertility in first group was from 1 to 11 years with a mean 6.2 years and in second group was from 1 to 18 years with a mean 4.5 years. In the first group, 80% (16 patients) had primary infertility and 20% (4 patients) had secondary infertility. In the second group, 77.3% (33 patients) had primary infertility and 22.7% (42 patient) had second infertility. The irregularity of menses in the first group was 65.0% and in second group was 63.3% before treatment (Table 1).

Figure 1

Table 1: Distribution of irregularity of menses in the two groups before treatment

Type of Menses	Groups				Total	
	CC+ Br		CC+ De		No	%
	No	%	NO	%		
Regular	7	35.0	8	36.4	15	35.7
Irregular	13	65.0	14	63.6	27	64.3
Total	20	100	22	100	42	100
Chisquare: P=0.927 (NS)						

CC – clomiphene citrate; Br – Bromocriptine; De - Dexamethasone

After treatment there was a significant effect on regularity of menses. In the first group, 68.2% had regular menses and in the second group 50.0% had regular menses (Table 2). The pregnancy rate was significantly different. In the first group it was 40.0% and in the second group 22.7% (Table 3).

Figure 2

Table 2: Regularity of menses in patients with previously menses irregularity in the two groups after treatment

Regular menses	Groups				Total	
	CC+Br		CC+De		No	%
	No	%	No	%		
Yes	9	68.2	7	50.0	16	59.3
No	4	31.8	7	50.0	11	40.0
Total	13	100	14	100	27	100
Chisquare:					P=0.533 (NS)	
Mc Nemar					P=0.0002(sig)	

Figure 3

Table 3: Pregnancy rates in the two groups

Pregnancy	Groups				Total	
	CC+Br		CC+De		No	%
	No	%	No	%		
Yes	8	40.0	5	22.7	13	31
No	12	60.0	17	77.3	29	69
Total	20	100	22	100	42	100
Chisquare:					P=0.381(NS)	
Mc Nemar:					P=0.002(sig)	

Table 4 shows the pregnancy rates in two groups based on the infertility type and Table 5 shows pregnancy rates in two groups based on the age. The pregnancy rate in two groups based on the duration of infertility is shown in Table 6. In this study the PCOD patients with adjunctive use of bromocriptine or dexamethasone required only low dose of clomiphene citrate for induction ovulation.

Figure 4

Table 4: Pregnancy rates in two groups based on the infertility type

Type of infertility	Pregnancy	Group				Total	
		CC+Br		CC+De			
		No	%	No	%	No	%
Primary	Yes	7	43.8	3	17.6	10	30.3
	No	9	56.3	14	82.4	23	69.7
	Total	16	100	17	100	33	100
Secondary	Yes	1	25	2	40	3	33.3
	No	3	75	3	60	6	66.7
	Total	4	100	5	100	9	100
Chisquare:		P=0.211(NS)		P=0.966(NS)			

Figure 5

Table 5: Pregnancy rate based on age in the two groups

Age		Groups				Total	
		CC+Br		CC+De		No	%
		No	%	No	%		
=< 23	Pregnancy						
	Yes	3	50	3	21.4	6	30
	No	3	50	11	78	14	70
	Total	6	100	14	100	20	100
>23	Pregnancy						
	Yes	5	35.7	2	25	7	31.8
	No	9	64.3	6	75	15	68.2
	Total	14	100	8	100	22	100
Chi-square:		P=0.225(NS)		P=0.966(NS)			

Figure 6

Table 6: Pregnancy rate based on the duration of infertility

Duration of infertility		Groups				Total	
		CC+Br		CC+ De		No	%
		No	%	No	%		
=< 3 years	Pregnancy						
	Yes	1	16.7	3	20	4	19
	No	5	83.3	12	80	17	81
	Total	6	100	15	100	21	100
>3 years	Pregnancy						
	Yes	7	50	2	28.6	9	42.9
	No	7	50	5	71.4	12	57.1
	Total	14	100	7	100	21	100
Chi-square:		P=0.861(NS)		P=0.640(NS)			

CONCLUSION

There are several options available for the 10-20% of women who fail to become pregnant after 6 months clomiphene therapy, in the absence of any other infertility factors. The two options are addition of dexamethasone or bromocriptine to clomiphene citrate. Dexamethasone 0.5mg at the bedtime to blunt the night time peak of ACTH, is added to decrease the adrenal contribution to circulating androgens and thus diminish the androgen level in micro-environment of the ovarian follicles. (4) One report indicated that even none-responders to clomiphene with normal

DHEA-S levels achieved ovulation and pregnancy with the addition of 10-day course of dexamethasone, begun concurrently with clomiphene. (5) Clinical experience suggests that successful induction of ovulation and achievement of pregnancy with bromocriptine can occur in the absence of galactorrhoea and with a normal prolactin level in women who failed to respond to clomiphene. (6,7,8,9) However this studies based on the nocturnal or latent hyperprolactinemia (10) The mechanism of bromocriptine action, may be an increase in follicular responsiveness either due to normalized elevated nocturnal serum prolactin level or suppression of LH.(3)

A decrease in LH may alter local follicular steroidogenesis in such a way as to create a more favorable micro-environment. All anovulatory infertile patients in this study had normal level of serum prolactin and normal level of DHEA-S. In our study, 68% of first group patients after treatment had regular menses (due to induction of ovulation) and pregnancy in 40% of patients was achieved. In this study 50% of second group of patients after treatment had regular menses (due to induction of ovulation) and pregnancy was achieved in 22.7% of patients.

An interesting relationship was found between adjunctive bromocriptine or dexamethasone to the clomiphene citrate that decreased the dose of clomiphene citrate needed for induction ovulation.

P.C.O.D is an anovulation disorder with biochemical and hormonal variation & dysfunction even in the presence of normal range of hormones. (11) From a practical point of view, treatment with bromocriptine and clomiphene citrate should precede the use of other methods of induction ovulation in PCOD patients with clomiphene citrate resistance. This treatment is of lower cost and lesser complexity and the tolerance is excellent if the dose is gradually increased to reach a final stable level.

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