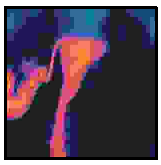

ORIGINAL PROF-629

HYPER PROLACTINAEMIC INFERTILITY;
CLINICAL TRIAL FOR THE MANAGEMENT AND COMPARISON BETWEEN TWO TREATMENT REGIMES

DR SOHAIL MAHMOOD CH. F.C.P.S.
Consultant Obstetrician & Gynaecologist
Senior Registrar Gynae Unit -2
Bahawal Victoria Hospital/Quaid-i-azam Medical College, Bahawalpur.

ABSTRACT

OBJECTIVE: To compare the success of two therapies, bromocriptine (parlodel) alone and bromocriptine in combination with clomiphene citrate in the treatment of infertile women with the diagnosis of hyperprolactinaemia to restore menstruation, onset of ovulation and to achieve pregnancy. **DESIGN**: Prospective study. **SETTING**. Bahawal Victoria Hospital Bahawalpur **PERIOD**:From1st June 1994 to 30th May 1995(one year study). **SUBJECTS**: Total of 58 patients were collected, of which, 18 lost contact in the initial visit, leaving 40 patients for analysis. In this study the patients included were with the biochemical diagnosis of hyperprolactinaemia associated with irregular, overdue periods and anovulatory cycles. Amenorrheic women with no evidence of ovarian estrogen production and elevated FSH levels were excluded. **RESULTS**: Total 40 patients were divided into two group. One group of 20 patients were given bromocriptine alone. Out of these, 19 patients restored menstruation (95%), 16 patients started ovulation (80%) and 13 patients conceived (65%).In the second group of 20 patients who were put on bromocriptine plus clomiphene citrate, the results turned out as restoration of menstruation in all 20 patients (100%),18 started ovulation(90%)and 15 patients conceived(75%). **CONCLUSION**: Hyperprolactinaemic infertile patients with menstrual irregularities and anovulatory cycles (in whom other causes of infertility were carefully excluded) show better response when clomiphene citrate is administered in combination with bromocriptine as compared to treatment with bromocriptine alone.

KEY WORDS: Hyperprolactinaemia, Infertility, Combined regime .

INTRODUCTION

In our country uncontrolled fertility and infertility are two major problems affecting women's health, quality of life, social and psychological status. On one hand, uncontrolled fertility contributes a major share to our maternal morbidity and mortality. On the other hand, infertility brings misery and insecurity to many women who fail to conceive, facing the threat of divorce. The diagnosis of infertility is usually made when conception has not occurred after one year of unprotected sexual exposure in a couple trying to achieve a pregnancy[1].

The World Health Organization has defined infertility as failure to conceive over 12 months of exposure and leaves a longer term residual incidence of infertility of 10-15%[2].

In many couples more than one factors may be operative. Recent important advancements have

increased the possibility of success in the treatment of infertility[3]. New concepts about the pathophysiology of the disorder (hyperprolactinaemia) have been introduced. In this regard, the role of prolactin in human reproduction is another newly discovered phenomenon. This has opened a new chapter in the management of infertility. Hyperprolactinaemia was found responsible for infertility in about 1/3rd of the women studied recently[4].

Once the Hyperprolactinaemia is treated, these women can achieve conception as do the normal ones[5]. Dopamine agonist drugs such as bromocriptine are highly affective in lowering prolactin level and restoring ovulation, irrespective of the etiology of hyperprolactinaemia[6,7].

In my clinical impression, ovulation / conception can be achieved in a shorter time period with greater safety and higher success rate. It is achieved if ovarian stimulant i.e Clomiphene Citrate is combined with dopamine agonist drugs. The results are especially encouraging in the treatment of such hyperprolactinaemic patients.

Infertility due to anovulation has remained an un-treatable disorder for a long time. Recent advances in reproductive endocrinology have led to a greater understanding of the mechanism regulating these processes. Failure of ovulation and secondary amenorrhoea may often be due to excess production of prolactin even in the absence of galactorrhoea[4,8,9]. There is no deficiency of gonadotrophins in this situation but the hyperprolactinaemia inhibits the ovarian response to the post pituitary gonadotrophic hormones. The reason for the frequent absence of galactorrhoea is that, other hormones such as oestrogen, progesterone, thyroxine and cortisone are necessary to prepare the breast for milk secretion in response to prolactin. Most of these patients , will respond to bromocriptine, a drug which stimulates dopamine receptors.

Dopamine is probably the hypothalamic factor that inhibits the release of prolactin from the pituitary. However, the treatment can be made more effective if ovarian stimulant therapy as clomiphene citrate is administered at the same time. In this way the inhibitory effect of prolactin on the release of GnRH is removed, increasing secretion of FSH and LH by the anterior pituitary[11,14]. These hormones will cause physiological stimulation of the ovaries. If we combine clomiphene citrate, it will further elevate the level of gonadotrophins by direct stimulation as well as lowering of inhibitory effect of estrogens on the hypothalamic-pituitary axis. Ovulation/ conception can be achieved in a shorter time period with greater safety and success rate by combination of dopamine agonist with ovarian stimulant therapy[5,6,13,14]. The basis of this study was my clinical impression that combined therapy would be more effective.

MATERIAL & METHODS

All infertile couples with infertility of variable duration reporting to our department, during the period of 1st June 1994 to 30th May 1995 were examined. After taking their history and doing complete physical and pelvic examination, investigations for infertility were carried out. Specific tests for male factor, tubal factor, ovulation and cervical factor were done.

Appropriate investigations

1 Baseline investigations
2 Blood examination for hormone profile (Serum Prolactin LH , FSH)
3 Hysterosalpingography(HSG)
4 Pelvic U.S.G. scan for ovarian morphology to exclude polycystic ovarian disease.
5 Diagnostic laparoscopy(Lap-Dye-Biopsy)

Inclusion Criteria

Only those cases with biochemical diagnosis of hyperprolactinaemia associated with irregular, overdue periods and anovulatory cycles were included in this study.

Exclusion Criteria

1 Amenorrhoeic women with no evidence of ovarian estrogen production and elevated F.S.H levels were ruled out.
2 In these patients, presence of pituitary adenoma was excluded by the established clinical, biochemical and radiological criteria. Clinical examination included objective testing of visual fields to rule out any visual field defects.
3 Biochemical tests for serum prolactin level were performed. Patients exhibiting prolactin level greater than 200 ng/ml were also excluded as such high levels are almost always due to an adenoma.

Biochemical diagnosis of hyperprolactinaemia was made when either overt or latent hyperprolactinaemia was defined as serum prolactin level equal to or more that 15 ng/ml. Latent hyperprolactinaemia was defined as normal resting prolactin level rising to more than or equal to 150 ng/ml, half hour after metoclopramide injection. Clinical examination included objective testing of visual fields to rule out any visual field defects. Plain x-ray skull for pituitary fossa was routinely performed. C.T. scan was not performed routinely for this purpose because of very high cost. The selected patients were assigned to one of these two groups randomly: One group was given Bromocriptine according to the continuous regime in a dose of 5 mg per day. (starting with a smaller dose and increasing gradually). Other group was given Bromocriptine in above mentioned dose plus clomiphene citrate(cerophene) starting with a dose of 50 mg/day for 5 days and then adjusting further dose according to the patient's response. Maximum dose given was 200 mg/day for 5 days of an anovulatory cycle of immediately after a progesterone induced bleeding episode. Patients were advised to have intercourse on alternate days on 10^{th} ,12^{th} ,14^{th} & 16^{th} days or according to the size of follicle ,being monitored on USG.

The therapy was given for six consecutive cycles and the patients were followed up at four weeks interval during this period. Patients were asked to maintain strict record of basal body temperature, menstrual calendar, galactorrhoea (if present) and any undesirable side effects as visual disturbances, headaches, gastrointestinal upsets, abdominal bloating or pain, etc. All these points were specifically checked at their follow up visits and clinical examination performed to see follicular size. Progress was noted in terms of establishment of regular menstrual cycle, evidence of ovulation and positive pregnancy test.

The following parameters were used to indicate ovulation.

1 Basal Body Temperature record showing a biphasic monthly pattern with elevation of 0.5-0.8 ½ F or about 0.3 ½ C during luteal phase.
2 Follicular tracking with T V S [Trans- vaginal ultrasound] OR with abdominal ultrasound.
3 Rise in serum progesterone to values > 5 ng/ml during premenstrual phase.
4 Secretory endometrium phase pattern seen in biopsy near the end of luteal phase.
5 Finding of thick, cellular cervical mucus that does not form a fern pattern.
6 Ovulation was considered as positive if any two of the above parameters were present.

Clinical evidence of positive pregnancy test and confirmation of gestational sac on ultrasound was the end point of the study.

RESULTS

A total of 58 patients were collected during one year(June1994-May1995),of these 18 lost contact in the initial visits leaving 40 patients for the analysis. These patients were assigned randomly to one of above mentioned two groups for infertility treatment so that 20 patients were placed in each group. Patients age ranged from 22 to 33 years. (mean age was 27.5 year).

Thirty four patients had primary infertility and six had secondary infertility. The duration of infertility was from 2 to 10 years. (mean 6 years).

Twelve patients had latent hyperprolactinaemia. In this group serum prolactin level ranged from 170 to 518 ng/ml. (mean 284.75ng/ml) ½ hour after injection of metoclopramide (Maxolon). In others the resting level was 15 to 120 ng/ml (mean 22.70).

All patients had irregular, overdue periods. However, 24 out of 40 patients already had menstruation without medication. While 16 had secondary amenorrhea and had withdrawal bleeding only after administration of progesterone (Primolut N). Six patients gave history of galactorrhoea while it could be clinically demonstrated in only two patients examined.

The results of success of therapy in the two groups were recorded in terms of re-establishment of periods, presence of ovulation and positive pregnancy test.

GROUP 1 (on Bromocriptine Therapy)

Results of Bromocriptine therapy in 20 infertile hyperprolactinaemic women with anovulatory cycles are presented in Table I.

Table-I. Pregnancy rate following bromocriptine in Hyperprolactinaemic infertile patients

	No.	Restored Menstruation	Proven ovulation	Pregnancies
Hyperprolactinaemia with irregular/overdue	20	19	16	13
Anavulatory cycles		95%	80%	65%

Table-II. Pregnancy rate following bromocriptine plus clomiphene citrate in Hyperolactinaemic infertile patients.

	No.	Restored Menstruation	Proven ovulation	Pregnancies
Hyperprolactinaemia with irregular/overdue	20	19	18	15
Anavulatory cycles		100%	90%	75%

GROUP-II (on Bromocriptine plus Clomiphene Citrate Therapy)

Results of bromocriptine plus clomiphene citrate therapy in 20 hyperprolactinaemic patients with anovulatory cycles treated for infertility are presented in Table II.

MEAN DURATION OF TREATMENT

Surprisingly no major difference was observed in both groups treated. The average time period between onset of therapy and conception was '4' months.

FREQUENCY OF SIDE EFFECTS

Most of the patients tolerated the therapy well and only four out of 40 treated patients complained of minor side effects. Two were on bromocriptine while two were taking combined regime.

FREQUENCY	
Side Effects	No. of Pts
Nausea & Vomiting	3
Abdominal Bloating at time of ovulation.	1

These symptoms occurred mostly at the beginning of treatment and decreased later.

DISCUSSION

The reported incidence of hyperprolactinaemia in infertile women is nearly 25%[4], 75 percent of patients with amenorrhea / galactorrhoea and 15% of all patients with menstrual disorders are found to have raised prolactin levels[7]. Alternatively, infertility is the most common clinical problem arising due to hyperprolactinaemia [8,13,14]. The purpose of my study was not to determine the prevalence of the disorder, yet the fact that we detected 58 such cases during a period of just one year. It shows that the disorder is quite common in our infertile patients.

We found that metoclopramide (maxolon) stimulation is quite helpful in picking up cases of latent hyperprolactinaemia who can also benefit from bromocriptine to overcome their problem of infertility. Our conception rate of 65% to 75% is consistent with that reported by various workers [11,14]. I think that regularity in the intake of the drug is also a factor in this regard. More than 20% of our patients were lost to follow up after initial one or two visits, highlighting poor patient compliance. Intolerance to the drug due to gastrointestinal upsets may be an additional factor. A small starting dose with subsequent increments may help to overcome this problem. Clinical parameters of onset of ovulation and pregnancy, like basal body temperature and change in menstruation are better employed to judge the outcome of the treatment .

In a fixed time period of 6 months of therapy, regular menstruation was restored in 100% patients with proven ovulation in 90% and successful conception in 75% patients on combined regime. In the same time period, a comparative study using bromocriptine alone showed restoration of regular menstruation in 95% of patients with proven ovulation in 80% and successful conception in 65% patients. There is a clear difference in success of therapy in terms of achievement of ovulation/conception

[8,11,12,13,14].

Finally, the results of the present study need to be interpreted in the light of its limitations, such as being relatively small sized, absence of controls and lacking in long term follow up.

Safety of the drugs with regard to teratogenecity remains an unanswered area of concern. The course and outcome of pregnancies was also not studied , as We are only interpreting the success of therapy in terms of confirmation of pregnancy. Thus the apprehension that maternal problems and fetal abnormalities might be higher in such cases, finds no support from our results. Effects of bromocriptine administration during pregnancy are constantly under debate. Our study could not provide any clue to this. A lot of concern has been expressed about the hazard of pituitary expansion during pregnancy in hyperprolactinaemic patients. I also closely observed my patients for the possibility of this happening but found no such effect. This might be because I screened my patients carefully for the presence of pituitary adenoma before the induction of ovulation[4,8,9]. Another reason might be that none of my patients had resting prolactin level greater than 120 ng/ml, and the likelihood of an adenoma at this level is quite low.

CONCLUSION

The study, though not is any way conclusive, does support the clinical impression that hyperprolactinaemic infertile patients with menstrual irregularities and anovulatory cycles (in whom other causes of infertility were carefully excluded) show better response when clomiphene is administered in combination with bromocriptine as compared to treatment with bromocriptine alone. The pregnancy induced in this manner does not pose undue risk to the mother as seen in follow up.

REFERENCES

1 Management of common problems in Obst & Gynae by Mischell & Brenner 2nd Ed. P. 1523.

2 C.R. Whitfield, Dewhurst, Textbook of 1995. P:551.

3 Morris Rs ; Sauer- MV New advances in treatment of infertility in women with ovarian failures cursopin - obstet-gynecol 1993 Jun; 5 (3) : 368 -77.

4 Molitch ME, Manifestations , epidemiology and Pathogenesis of Prolactinomas in Women. OLefsky JM, Robbins RJ eds Prolactinamas. New York, Churchill livigstone 1986.

5 Haider . P. Bromocriptine tie in Obstetrics and Gynaecology J.P.M.A. 1990; 224-28.

6 Johnston DD, Prescott RWG, Kendalt JP, Hal K. Crombie AL Hyperprolactinaemia. Long term effects of bromocriptine Am. J. Med. 1983; 75, 868.

7 Blankstein J, Mashiachs, Lunenfeld B. eds ovulation induction and in-vitro fertilization. Chicago year book Medical publishers 1988; 77-82.

8 Archer DF : Hyperprolactinaemia In : Behermen SJ, Kistner RW, Patton Gw eds. Progress in infertility. Boston Little Brown & Co. 1988: 463-73.

9 Asuki K, Uemura T, Minaguchi H. Occult hyperprolactinaemia in infertile women. Fertil-Steril. 1993 Sep; 60(3) :423-7.

10 Scot RT, Leonordi MR, Hofman GE, Illinois EH; Neal GS, Navot DA. Prospective evaluation of clomiphene citrate challenge test. Screening of general infertility population. Obstet. Gynaecol, 1993 oct ; 82(4 pti) : 539-44.

11 Amos WL. Successful treatment of infertility with Bromocriptine mesylate after failure of clomiphene in anovulatory patients. Advance therapy 1984(1): 343-8.

12 Dhaliwal LK, Khera KR, Gupta I. Hysterosalpingography in the evaluation of tubal factors. Pak. Jr. Obstet & Gynaecol 1990; 3(1) : 8-12.

13 Fehmida Naheed. Bromocriptine: Effect on galactorrhoic hyperprolactenaemic women. JCPSP 1999, Vol. 9 (1): 28-31.

14 Aisha Malik & Fakhar-un-Nisa Chaudry. Comparison of different treatment regimens in infertile women with hyperprolactinaemia.JCPSP 1999, Vol. 9 (1): 32-34.