

TREATMENT OUTCOME OF HYPERPROLACTINAEMIC INFERTILITY WITH CARBEGOLINE IN SUB SAHARAN AFRICA

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ABSTARCT

Objectives: Hyperprolactinaemia is a known cause of infertility. We explored the efficacy of carbegoline, the long acting dopamine agonist that was recently introduced into our medical practice.

Methodology: Seventy six patients with infertility secondary to hyperprolactinaemia were studied over a period of 20 weeks each. All the patients had carbegoline twice weekly for eight weeks. Two dosage regimen were used based on the pretreatment prolactin level; less than 50ng/ml had 0.25mg twice weekly (n=58) and 50ng/ml and above 0.5mg twice weekly (n=18).

Results: Normalization of prolactin level was achieved in 75 (98.7%) patients. At the end of the study period, there was resumption of menstrual flow in 10 (76.9%) of the 13 patients that were amenorrhoeic and all the 39 (100%) patients that were oligomenorrhoeic had their normal menstrual cycle restored. Resumption of ovulatory cycles occurred in 87.7% of those with anovulatory cycles. Of the 76 patients, 69 (90.8%) got pregnant during the 20 weeks study. However, out of the 69 that got pregnant, 13 (18.8%) got pregnant while on carbegoline therapy. There was no case of carbegoline resistance or discontinuation recorded in this study.

Conclusion: Carbegoline is a cost effective first line therapy in the management of infertile women with hyperprolactinaemia.

KEYWORDS: Carbegoline, Female infertility, Hyperprolactinaemia, Pregnancy.

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INTRODUCTION

Infertility is an important gynaecological condition in Africa. It is associated with social and psychological consequences because the society places a high premium on fertility. The prevalence of infertility ranges from 20 - 46% in parts of West Africa^{1,2} and it accounts for 45 - 65% of gynaecological consultation.^{3,4} Ovulatory problems are less common cause of female infertility in subsaharan Africa, compared to tubal pathology which is mostly secondary to sexually transmitted disease.¹ However, emerging result from study done in North Eastern region of Nigeria showed an increase

in the trend of hyperprolactinaemia amongst infertile females; they reported a prevalence of 31.7%.⁵

In Nigeria, due to non availability of carbegoline and quinagolide heretofore the medical treatment of hyperprolactinamia had centered only on the use of bromocryptine. However, with the introduction of carbegoline, we decided to evaluate its effectiveness in the management of hyperprolactinaemic infertile females.

METHODOLOGY

Over a period of 40 months, we prospectively studied 76 consecutive infertile women with hyperprolactinamia that fulfilled our inclusion criteria. These inclusion criteria were as follows:

1. Serum prolactin level of 20ng/ml and above.
2. Absence of other causes of infertility apart from hyperprolactinamia and anovulation.
3. Absence of contraindication to the use of carbegoline.
4. Non use of bromocryptine in the last three months.
5. Duration of infertility greater than a year.

Radioimmunoassay method of hormone assay was used to measure serum prolactin and values were expressed in nannogram per milliliter (ng/ml). Serum prolactin was measured before commencement of treatment and at weeks 8, 14 and 20 from initiation of treatment. The dose of carbegoline given to the patients was based on the baseline serum prolactin level. Patients with prolactin levels less than 50ng/ml were given 0.25mg twice weekly and those with levels of 50ng/ml and above had 0.5mg of carbegoline twice weekly. The treatment lasted eight weeks.

The patients were followed up for 20 weeks from the initiation of treatment. During the study period, pelvic sonogram was done monthly (day 10 or 11 of menstrual cycle) for evidence of ovulation. We also looked for side effects, the effect of the drug on the gonadal functions and fertility. Whenever pregnancy occurred while on treatment, carbegoline was

stopped. After 8 weeks of carbegoline treatment, patients who still had anovulatory cycles with normal prolactin level were placed on clomiphene citrate for ovulation induction.

RESULTS

During the study period, of the 76 patients that were enrolled, 40.8% (31 patients) presented with primary infertility and 59.2% (45 patients) with secondary infertility. The mean age of the patients was 33.4 years with a range of 22 to 43 years. Baseline serum PRL level showed 58 (76.3%) patient had levels less than 50ng/ml, fifteen (19.7%) patient had levels between 50 and 100ng/ml and the remaining three (3.9%) patients had serum PRL levels greater than 100ng/ml.

The commonest menstrual disorder was oligomenorrhoea occurring in 39 (51.3%) patients; this was followed by secondary amenorrhoea in thirteen (17.1%) patients. Normal menstrual cycle and flow was recorded in 24 (31.6%) patients. Of the 76 patients, 63 (82.9%) had galactorrhoea and 57 (75%) were found to have anovulatory cycles (Table-I). Except one patient who had the dose of carbegoline reduced to 0.25mg twice weekly due to severe headache and irritability, all the patients completed their treatment with the prescribed

Table-I: Profile of patients

Variables	N = 76	%
Types of infertility		
Primary infertility	31	40.8
Secondary infertility	45	59.2
Baseline serum PRL		
<50ng/ml	58	76.3
50 – 100ng/ml	15	19.7
101 – 149ng/ml	3	3.9
Menstrual history		
Normal menstrual cycle/flow	24	31.6
Secondary amenorrhoea	13	17.1
Oligomenorrhoea	39	51.3
Presence of anovulatory cycle	57	75.0
Presence of galactorrhoea	63	82.9
PRL – Prolactin		

dosage of cabergoline. At the end of the eight week treatment with cabergoline, 75 (98.7%) of the 76 patients had their serum prolactin levels restored to normal. The remaining one patient with baseline serum prolactin greater than 100ng/ml, had her serum prolactin level reduced to 43ng/ml. Galactorrhoea had disappeared in the 63 patients that presented with it. Amongst the 52 patients that presented with menstrual disorder, there were restoration of normal menstrual flow in 39 (75%) of them by the end of the 12th week and in fifty (96.2%) by the end of the 20 week study. Three (3.8%) patients with menstrual disorder at the end of the study had presented with secondary amenorrhoea before commencement of treatment with cabergoline. Two of the three patients had normalization of their prolactin level by the end of the study period. Ovulatory cycles had resumed in 50 (87.7%) of the 57 patients with anovulatory cycles at the 12th week of study. Of the seven patients with persistent anovulation, four (57.1%) responded to ovulation induction with clomiphene but the remaining three (42.9%) patients did not respond (Table-II). A pregnancy rate of 90.8% (69 patients) was recorded at the end of the 20 weeks study. However, thirteen (18.8%) patient got pregnant while on cabergoline and the drug was immediately discontinued (Table-II). Of the 69 patients that got pregnant, 61 have delivered healthy babies with one set

of twin inclusive, one first trimester miscarriage was recorded and the remaining seven patients had an ongoing pregnancy.

Side effects were recorded in seven (9.2%) patients. The side effects were not severe enough to call for discontinuation of treatment. However, one patient had her dosage of cabergoline reduced on account of severe headache and irritability.

DISCUSSION

Medical management is the first line therapy in the treatment of hyperprolactinaemia. This involves the use of dopaminergic drugs with prolactin lowering properties. The three dopamine agonist available for treatment of hyperprolactinaemia are bromocryptine, quinagolide and cabergoline. Hitherto, bromocryptine was the sole drug available for treatment of hyperprolactinaemia in our setting. However, the low efficacy and high discontinuation rate associated with bromocryptine due to its intolerable side effects;⁶ made the introduction of cabergoline into our clinical practice a highly welcome development.

Cabergoline is an ergot derivative with high affinity for D2-receptors and low affinity for D1-receptors.⁷ It has a half life of 65 hours and a duration of action of seven to 14 days, thus making the frequency of administration limited to once or twice weekly.^{7,8} Dose regimen

Table-II: Outcome of treatment with cabergoline

<i>Variables</i>	<i>Propotion</i>	<i>%</i>
Restoration of serum PRL to normal level	75 / 76	98.7
Disappearance of galactorrhoea	63 / 63	100
Resumption of normal menstrual cycle / flow		
at 12 th week of treatment	39 / 52	75.0
at 20 th week of treatment	50 / 52	96.2
Resumption of ovulatory cycle	50 / 57	87.7
Attainment of pregnancy	69 / 76	90.8
Time of conception		
During therapy with cabergoline	13 / 69	18.8
After therapy with cabergoline	56 / 69	81.2

of a drug has been documented to affect compliance with medications.⁹ The twice weekly dosage schedule of carbegoline encouraged patient compliance. We recorded 100% compliance rate in this study. This may be due to the few side effects and the relatively high cost of carbegoline. Patients had to purchase the drugs with their own money since we do not have an effective health insurance in place. Experience from similar study has also reported good compliance with carbegoline.⁶ From our series, the two dosage regimen of carbegoline employed was effective in stabilizing prolactin level in all patients but one. Other authors have reported similar dose range as effective.^{6,10} The effectiveness of the total dose of carbegoline (0.5 – 1mg given twice weekly) used in this study may however be related to the baseline serum prolactin of our patients, which were mainly less than 100ng/ml. Experience from earlier studies equally found women with low pre-treatment prolactin levels often achieving normal values during treatment with carbegoline.^{6,10} The aforementioned may also explain the 98.7% success achieved regarding normalization of prolactin level. Other studies reported prolactin normalization rates between 90 - 96% with carbegoline therapy.^{6,11,12}

We confirmed the efficacy of carbegoline in restoring ovarian functions. We found continued improvement with treatment throughout the study period, resulting in resumption of normal menstrual flow and restoration of normal menstrual cycle among patients that presented with amenorrhoea and oligomenorrhoea respectively. The 96.1% success recorded at the end of the study is similar to results of other authors.^{6,11,13} Additionally, resumption of ovulatory cycles in those patients that were previously anovulatory, corresponds to reported rates from similar studies.^{6,11,13}

Another important finding is the high pregnancy rate we recorded in our study; this can be explained by our study population being hyperprolactinaemic infertile women specifically. Other studies with no-specificity to infertile women as study population had quoted lower pregnancy rates^{6,10,11} Although

inconclusive, evidence from some studies have associated exposure to carbegoline at conception and in early pregnancy with good safety profile.^{10,14} There was no teratogenic effect recorded in our study. More importantly, there was no record of carbegoline resistance in our series. Though the mechanism of resistance to dopamine is not well understood, the most logical hypothesis is the reduction in dopamine receptor – binding sites.¹⁵ To substantiate this hypothesis, response to carbegoline and quinagolide has been reported to be less in subset of patients with prior bromocryptine resistance.^{10,16,17} Although 23 patients in our series had prior treatment with bromocryptine they did not fulfill the criteria to classify them as bromocryptine resistance. Resistance to bromocryptine occurs when there is persistent elevation of prolactin level and absence of improvement in clinical symptoms despite daily long term administration of 15 – 30mg of bromocryptine.¹⁸ The maximum daily dose of bromocryptine our patients were exposed to was 5mg. Intolerance to side effect is a major reason for dopamine agonist discontinuation. Although results of research conducted on carbegoline showed 0 – 3% discontinuation rate,^{6,19} we did not record any case of discontinuation in our series. The twice weekly dosing of carbegoline offers an improvement in success of treatment when compared to multiple daily dosing of bromocryptine and once daily dosing of quinagolide.

Limitation of the study: It is the selection bias of patients enrolled for the study as only those patients that could afford carbegoline were enrolled after fulfilling the inclusion criteria.

CONCLUSIONS

We found carbegoline to be a unique dopamine agonist. The good attributes of carbegoline in terms of pharmacokinetics and its efficacy in normalizing ovarian function, makes it a cost effective drug in the management of infertile women with hyperprolactinaemia.

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