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Effects of Carbegoline and Bromocriptine on Prolactin, Progesterone, Luteinizing and Follicle Stimulating Hormones in Hyperprolactinaemic Infertile Women in Orlu, Nigeria

Ajaero, Oluchi Chinwe[1]; Unekwe, Prince Chiazor[1]; Ajaero, Nnaemeka Uchendu[2]

[1]Department of Pharmacology and Therapeutics, Nnamdi Azikiwe University, Awka, Nigeria
[2]Department of Medical Laboratory Science, Imo State College of Health and Management Sciences, Amaigbo, Nigeria

ABSTRACT

This was an interventional study which evaluated the effects of bromocriptine and carbegoline on prolactin, progesterone, luteinizing and follicle stimulating hormones in hyperprolactinaemic infertile female subjects in Orlu, South-East Nigeria.

Hyperprolactinaemic females who were attending Gynaecology Clinic at Imo State University Teaching Hospital (IMSUTH) Orlu participated in the study. The participants were divided into two groups. Group A: 30 hyperprolactinaemic females were administered 1.25mg bromocriptine at night for the first one week; 2.5mg at week two; then 2.5mg twice daily for eighteen weeks. Group B: 30 hyperprolactinaemic females were administered 0.25mg carbegoline twice weekly for eight weeks. Serum prolactin, progesterone, LH and FSH were assayed before and after treatment using enzyme linked immunesorbent assay (ELISA) kits. The significant difference between the mean values of prolactin, LH, FSH and progesterone, in the pre and post treatment with carbergoline and bromocriptine was determined by paired t-test. Independent student t-test was used to compare between the two treatments. P value <0.05 was considered as statistically significant.

KEYWORDS: *Carbegoline, BromocriptinePregnancy, Prolactin and Infertility*

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The pre-treatment hormone levels for group A were: 57.35 ± 31.22ng/ml, 5.15 ± 3.32ng/ml, 3.65 ± 0.58miu/ml and 2.48 ± 0.57miu/ml, for prolactin, progesterone, FSH and LH respectively. The post-treatment values of the same hormones were: 17.20 ± 7.57ng/ml, 14.31 ± 5.06ng/ml, 5.41 ± 1.60miu/ml and 4.38 ± 1.52miu/ml. The pre-treatment hormone levels for group B were: 56.42 ± 22.66ng/ml, 2.91 ± 2.93ng/ml, 3.34 ± 1.77miu/ml, and 2.85 ± 1.50miu/ml for prolactin, progesterone, FSH and LH respectively, while the post-treatment values were 11.11 ± 3.64ng/ml, 13.8 ± 5.04ng/ml, 5.62 ± 0.74miu/ml and 5.22 ± 1.76miu/ml respectively. There was a statistically significant reduction in the prolactin level in group B (79.3%) after eight weeks of treatment compared to the group A (62%) after twenty weeks of treatment ($p<0.05$). Normalization of prolactin level was achieved in 100% women in group B and in 96.6% women in group A after treatment. There was significant reduction of prolactin levels and elevation of progesterone, LH and FSH in the post treatment values of the two groups.

Bromocriptine and carbegoline normalized the levels of prolactin after treatment. Administration of bromocriptine and carbegoline also increased the post treatment values of FSH, LH and progesterone. Therefore, bromocriptine and carbegoline have proven to be useful in the treatment of hyperprolactinaemic infertile women in Orlu, South East Nigeria. Hyperprolactinaemic infertile women who can afford carbegoline should not deny themselves access to carbegoline which brings the same effect with bromocriptine within a short

duration of time or otherwise should use bromocriptine.

INTRODUCTION

Fertility is important to all societies (19). Infertility is a common reproductive health issue with incidence ranging from 20% to 46% in parts of West Africa and it accounts for 45-65% of gynaecological consultations (29). Infertility can be due to myriads of factors such as genetic, anatomic, hormonal and immunological problems. It could also arise from secondary sources like sexually transmitted infections, surgery and obesity (27). Hormonal factors are the less common cause of female infertility in sub-Saharan Africa, compared to tubal pathology, which is mostly secondary to sexually transmitted disease (29). Sex hormones play a crucial role in reproductive biology as well as in general physiology. The most important aim of sex hormones is to design the cycle and to produce an optimal environment for pregnancy- follicular growth, ovulation, and corpus luteum formation and endometrial response including proliferative and secretory phase for implantation (5).

During the reproductive years, the pituitary gland in the brain generates hormones (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) that cause a new egg to mature and be released from its ovarian follicle. As the follicle develops, it produces the sex hormones oestrogen and progesterone, which thicken the lining of the uterus. Progesterone levels rise in the second half of the menstrual cycle, and following the release of the egg (ovulation), the ovarian tissue that replaces the follicle (the corpus luteum) continues to produce oestrogen and progesterone.oestrogen is the hormone that stimulates growth of the uterine lining (endometrium), causing it to thicken during the pre-ovulatory phase of the cycle (13). Ovulation occurs at about day 14 of a 28-day cycle. Oestrogen levels rise as a result of increasing oestrogen production by hormonally active cells within the follicle. Oestrogen levels reach a critical point at which oestrogen begins to exert positive feedback on the hypothalamus and pituitary, leading to an LH surge. The LH surge increases intra-follicular proteolytic enzymes, weakening the wall of the ovary and allowing for the mature follicle to pass through. The surge also causes the luteinization of thecal and granulosa cells which increases progesterone levels and begins the development of the corpus luteum. Once the follicle is released, it is caught by the fimbriae of the fallopian tubes. The oocyte remains in metaphase of meiosis II. It will complete meiosis II after fertilization (22).

The luteal phase lasts from day 14 to 28 of a typical cycle. It begins with formation of the corpus luteum and ends in pregnancy or luteolysis (destruction of the corpus luteum). FSH and LH stimulate what remains of the mature follicle after ovulation to become the corpus luteum. The corpus luteum grows and secretes progesterone and some oestrogen, which make the endometrium more receptive to implantation. If fertilization does not occur, progesterone and oestrogen levels fall, and the corpus luteum dies. These falling hormone levels stimulate FSH to begin recruiting follicles for the next cycle. If fertilization does occur, human chorionic gonadotropin (hCG) produced by the early placenta preserves the corpus luteum, maintaining progesterone levels until the placenta is able to make sufficient progesterone to support the pregnancy (22).

One of progesterone's most important functions is to cause the endometrium to secrete special proteins during the second half of the menstrual cycle, preparing it to receive and nourish an implanted fertilized egg. If implantation does not occur, oestrogen and progesterone levels drop, the endometrium breaks down and menstruation occurs (4). If a pregnancy occurs, progesterone is produced in the placenta, and levels remain elevated throughout the pregnancy. The combination of high estrogen and progesterone levels suppress further ovulation during pregnancy. Progesterone also encourages the growth of milk-producing glands in the breast during pregnancy (20). High progesterone levels are believed to be partly responsible for symptoms of premenstrual syndrome (PMS), such as breast tenderness, feeling bloated and mood swings. When a period is skipped, it could be because of failure to ovulate and subsequent low progesterone level (20).

Hyperprolactinaemia is the most common endocrine disorder. It occurs more frequently in women than in men. The clinical symptoms of hyperprolactinaemia are amenorrhoea, oligomenorrhoea, infertility, and galactorrhoea in women; decreased libido and impotence in men (2). Hyperprolactinaemia can be associated with significant morbidity. It is characterized by the presence of high level of prolactin in the blood (3). High prolactin can make it difficult for a woman to get pregnant. High prolactin levels can interrupt the normal production of the hormones oestrogen and progesterone. This can cause the ovaries to release eggs irregularly or stop altogether (12).

Elevated prolactin levels can result from physiological causes, such as pregnancy and stress, and pharmacological causes, including the use of neuroleptics, oestrogens, opiates, antihypertensive drugs or calcium channel blockers. Once physiological and iatrogenic stimuli have been

eliminated as causes of elevated prolactin levels, the presence of a micro- or macroprolactinoma is the most likely cause of persistent pathological hyperprolactinaemia. Symptoms of hyperprolactinaemia include signs of gonadal dysfunction, and female patients frequently present with oligomenorrhoea, amenorrhoea and galactorrhoea. Dopamine agonists are the preferred treatment for most patients with hyperprolactinaemic disorders; these agents are extremely effective in lowering serum prolactin levels, eliminating galactorrhoea, restoring regular menses and decreasing tumor size. Mimicking the action of dopamine, dopamine agonists, including bromocriptine, quinagolide and cabergoline differ in their efficacy and tolerability (7).

Bromocriptine is a semisynthetic ergot derivative of ergoline, a dopamine D_2 receptor agonist with agonist and antagonistic properties on D_1 receptors. Because of its short half-life (3.3 hours), bromocriptine may require multiple dosing throughout the day. Approximately 12 percent of patients are unable to tolerate this medication at therapeutic dosages. The most common adverse effects are nausea and vomiting, headache, dizziness and decrease in blood pressure. Bromocriptine administration via the vaginal route may reduce the incidence of side effects and offer an alternative to oral bromocriptine. A range of 5-18% of patients have been reported as resistant to bromocriptine treatment, with only partial lowering of plasma prolactin levels and an absence of tumor shrinkage (1).

Cabergoline is an ergoline derivative with a high affinity and selectivity for D_2 receptors. It has an extremely long plasma half – life of about 65 hours allowing once- or twice – weekly administration. Unlike bromocriptine, cabergoline has low affinity for D_1 receptors. Cabergoline is more expensive than bromocriptine, and some physicians may reserve the medication for use in patients who are resistant to or intolerant of bromocriptine. Cabergoline may be administered at doses ranging between 0.5 and 1.5 mg once or twice per week. The drug dosing is less frequent and the drug is more tolerable, patient compliance may be better with cabergoline than with bromocriptine. The current recommendation is to discontinue cabergoline one month before attempting conception, although no detrimental effects on foetal outcomes in more than 300 pregnant women on cabergoline have been reported (17).

Bromocriptine has been the reference compound and effectively suppresses prolactin secretion, restores gonadal function, and shrinks prolactinomas. Its half-life is short so that it has to be given two or three times daily. Cabergoline is a new, selective, potent and long-lasting dopamine agonist that inhibits prolactin secretion in both normal subjects and those with hyperprolactinaemia, with duration of action of up to 21 days after single oral doses of 0.3-1.0 mg (16).

MATERIALS AND METHODS

Drugs and Sources

Cabegoline manufactured by Pfizer Ilaclar Limited, Sti 34347 Ortakoy- Istanbul, UretimYeri Pfizer Italia s.r.i Ascoli Piceno, Italy and Bromocriptinemanufactured by MedaPharma SL Av. Castilla, 2 (P.E, San Fernando) 28830 San Fernando Henares (Madrid) were used in this study.

Equipment and sources

Prolactin, FSH and LH Accubind ELISA test kits from Monobind Incorporated, Lake forest, CA 92630, USA and progesterone kit from Inteco Diagnostics, Unit B1, 62, Beechwood Road London E8 3DY United Kingdom were used in the study. ELISA Analyser produced by Accurex Diagnostic (11312 Lbj Free Way, Suite 500 Dallas, Texas 75238 USA) installed at Imo State University Teaching Hospital (IMSUTH) was used in this study.

Cotton wool by A and B Quality Ventures, 125 Sharada industrial layout, Face 3, Kano State Nigeria; Sterile sample containers and syringes manufactured by Jiangsu Zhenkang medical apparatus company limited, Sanhekou Zhenglu town Changzhou Jiangsu China and methylated spirit by New Healthway company limited km.22, Bagagry express way, Ajangbadi, Lagos, Nigeria were all used.

Study design

This interventional study evaluated the effects of bromocriptine and carbegoline on prolactin, progesterone, luteinizing and follicle stimulating hormones in hyperprolactinaemic infertile female subjects in Orlu, South-East Nigeria. Every woman was counselled by the researcher; clinically assessed by the clinical Coordinator and the blood samples of consenting women were collected for hormone assay (prolactin, progesterone, FSH, and LH). Those with prolactin levels above 25ng/ml were recruited into the study after they had been guided to fill questionnaires in order to get their complete history, diet and medications. Each woman was assigned to one of the study groups in a random fashion. Randomization method was performed by placing thick coloured pieces on drug envelopes in a black bag - red for cabergoline and blue for bromocriptine. Each woman withdrew from the bag. The participants were divided into two groups. Group A: 30 hyperprolactinaemic females were administered 1.25mg bromocriptine at night for the first one week; 2.5mg at week two: then

2.5mg twice daily for eighteen weeks. Group B: 30 hyperprolactinaemic females were administered 0.25mg carbegoline twice weekly for eight weeks. Subjects in each group took the same dose. They were educated on how the drugs would be taken. Subjects were followed up until they came for post treatment tests. Serum prolactin, progesterone, luteinizing and follicle stimulating hormones (LH and FSH) were measured before and after treatment at IMSUTH Clinical Chemistry Laboratory, using enzyme linked immunosorbent assay (ELISA) kits. Hormone levels of the participants in Group A were also estimated at two months before the continuation of therapy. Blood samples for the estimation of serum prolactin, luteinizing and follicle stimulating hormones were collected on day 2-3 of the women's cycle while samples for progesterone estimation were collected on day 21. A volume of 5ml of blood sample was asceptically collected from a peripheral vein (antecubital venipuncture) and dispensed into a plain container. The blood was allowed to clot, spun at 4000 rpm for 10 minutes to obtain a clear serum, which was separated into a plain container and used for analysis. Control subjects were women of reproductive age who were neither pregnant nor breastfeeding.

Inclusion Criteria:
Consenting infertile women with hyperprolactinaemia with or without galactorrhoea who completed their medication and came back for the post treatment tests.

Exclusion criteria:
Infertile women with normal prolactin levels; infertile women with hyperprolactinaemia who did not give consent and those that did not return for post treatment test. Infertile women with hyperprolactinaemia receiving treatment for galactorrhoea prior to presentation, menopausal women, and subjects on anti-psychotics, anti-emetics, tricyclic antidepressants, glutamide, amiodarone, methyldopa, and cimetidine were excluded.

Ethical clearance
The study was approved by the Ethics committee of Imo State University Teaching Hospital (IMSUTH) Orlu, South East Nigeria.

RESULTS

Recruitment of Subjects

A total of 72 women (test subjects) were recruited for the study. 24 out of the 72 women were students; 30 were government workers (health workers and teachers); 18 were self-employed. 36 women were enrolled in both GROUP A (women on treatment with bromocriptine) and GROUP B (women on treatment with carbegoline). 83% (60 women: 30 in each group) completed the study. 17% did not complete the study (3 women in group A and 6 women in group B due to pregnancy resumption and 3 in group A for loss to follow up). Control subjects were 30 in number among which 15 were government workers, 10 were self-employed and 5 were students. The women in each group were comparable in terms of age: average age for group A was 33.5years; 30.9years for group B; 32.0years for the control group. The women in each group were comparable in terms of diet consumed.

Biochemical Analysis

Serum prolactin, progesterone, LH and FSH were assayed before and after treatment using enzyme linked immunesorbent assay (ELISA) kits according to manufacturer's instruction. All reagents were from Accubined except that for progesterone which was from fromInteco Diagnostics UK.

Table 1 AGE DISTRIBUTION OF THE INFERTILE HYPERPROLACTINAEMIC WOMEN

Age (in years)	Bromocriptine group	Cabergoline group	All
≤20	1 (3.3)	4 (13.3)	5 (8.3)
21-30	5 (16.7)	10 (33.4)	15 (25.0)
31-40	18 (60.0)	12 (40.0)	30 (50.0)
≥41	6 (20.0)	4 (13.3)	10 (16.7)
Mean±SD	**34.3 ± 6.8**	**30.9 ± 7.7**	**32.6 ± 7.4**

SD = standard deviation.

Table 2 COMPARISON OF PROLACTIN, PROGESTERONE, FSH AND LH LEVELS OF HYPERPROLACTINAEMIC INFERTILE FEMALE AND NORMOPROLACTINAEMIC FEMALE

Hormone	Hyperprolactinaemic female Mean ± SD	Normoprolactinaemic female Mean ± SD	t-test	P value
Prolactin (ng/ml)	56.88 ± 27.05	13.8 ± 4.6	12.34	<0.001
FSH (miu/ml)	3.50 ± 1.31	6.5 ± 2.8	17.70	<0.001
LH (miu/ml)	2.67 ± 1.14	4.0 ± 1.2	9.07	<0.001
Progesterone (ng/ml)	4.03 ± 3.31	6.4 ± 2.3	5.55	<0.001

***Secondary data - Digbanet al (2018)**

Table 3: LEVELS OF PROLACTIN, PROGESTERONE, LH AND FSH OF HYPERPROLACTINAEMIC INFERTILE FEMALE BEFORE AND AFTER TREATMENT WITH BROMOPCRIPTINE

Hormone	Before Treatment Mean ± SD	After Treatment Mean ± SD	t- test	P value
Prolactin (ng/ml)	57.35 ± 31.22	17.20 ± 7.57	6.41	<0.001
FSH (miu/ml)	3.65 ± 0.58	5.41 ± 1.60	9.92	<0.001
LH (miu/ml)	2.48 ± 0.57	4.38 ± 1.52	17.51	<0.001
Progesterone (ng/ml)	5.15 ± 3.32	14.31 ± 5.06	7.53	<0.001

SD = standard deviation.

Table 4: LEVELS OF PROLACTIN, PROGESTERONE, LH AND FSH OF HYPERPROLACTINAEMIC INFERTILE FEMALE BEFORE AND AFTER TREATMENT WITH CABERGOLINE

Hormone	Before Treatment Mean ± SD	After Treatment Mean ± SD	t- test	P value
Prolactin (ng/ml)	56.42 ± 22.66	11.11 ± 3.64	12.37	<0.001
FSH (miu/ml)	3.34 ± 1.77	5.41 ± 1.60	12.04	<0.001
LH (miu/ml)	2.85 ± 1.50	5.22 ± 1.76	7.26	<0.001
Progesterone (ng/ml)	2.91 ± 2.93	13.81 ± 5.04	8.28	<0.001

SD = standard deviation.

Table 5: COMPARISON OF MEAN DIFFERENCE IN LEVELS OF PROLACTIN, PROGESTERONE, LH AND FSH OF HYPERPROLACTINAEMIC INFERTILE FEMALE SUBJECTS FOLLOWING TREATMENT WITH CABERGOLINE ANDBROMOCRIPTINE

Hormone	Bromocriptine group Mean difference Mean ± SD	Cabergoline group Mean Difference Mean ± SD	t- test	P value
Prolactin (ng/ml)	40.14 ± 34.32	45.31 ± 20.06	0.71	0.48
FSH (miu/ml)	1.97 ± 0.62	2.06 ± 1.56	0.32	0.75
LH (miu/ml)	1.90 ± 1.38	2.37 ± 1.56	1.23	0.22
Progesterone (ng/ml)	9.16 ± 5.07	10.90 ± 4.96	1.34	0.18

SD = standard deviation.

Table 6: COMPARISON OF PERCENTAGE CHANGE IN LEVELS OF PROLACTIN, PROGESTERONE, LH AND FSH FOLLOWING TREATMENT WITH CABERGOLINE ANDBROMOCRIPTINE

Hormone	Cabergoline Change in level (%)	Bromocriptine Change in level (%)	t-test	P value
Prolactin	79.3	62.0	4.11	<0.001
FSH	107.6	55.8	1.99	0.05
LH	114.8	80.1	1.41	0.17
Progesterone	1019.9	814.2	0.46	0.65

% = percent

Discussion

This study found that there was significant decrease in post treatment with cabergoline and bromocriptine drugs compared with pre-treatment groups regarding the mean values of serum prolactin hormone (tables 3 and 4). This result matches with the results got by (2,7) who mentioned that the dopamine agonists have become the treatment of choice for the majority of patients with hyperprolactinaemic disorders. This is because the dopamine agonists have a similar mode of action to dopamine in stimulating dopamine receptors on the prolactin-secreting pituitary cells and the stimulation of these receptors leads to inhibition of both prolactin secretion and synthesis. This finding have been well supported with data published by other studies (1,3,30,23).

The data obtained from the present study revealed that cabergoline and bromocriptine are both effective in the treatment of hyperprolactinaemic infertility with regard to prolactin reduction. The efficacy of bromocriptine has been evaluated in previous studies (1,3,30). These authors demonstrated the benefit of bromocriptine in lowering serum prolactin level in the majority of patients, which are in agreement with the results of this study. The percentage of reduction of serum prolactin level obtained in the present study in bromocriptine group is 62%. Regarding cabergoline, the current results are in agreement with several other

studies reported over the years demonstrating the efficacy of cabergoline treatment in hyperprolactinaemia (1,3,30). The percentage of reduction of serum prolactin level obtained in the present study in cabergoline group is 79.30%. Cabergoline normalized prolactin levels in 100% of subjects whereas bromocriptine normalized prolactin in 96% of subjects. The result got for both drugs is close to the findings in a retrospective study of 455 patients, in which cabergoline normalized prolactin levels in 92% of patients with idiopathic hyperprolactinaemia or a microprolactinoma and in 77% of 181 patients with macroadenomas (28). The percentage of normalization of prolactin for the bromocriptine group in the present study is higher than that (67.7%) reported by (1) and also better than the results obtained by (18) where the success rate was only 59%. The percentage of normalization of prolactin for the carbegoline group is higher than that (87.7%) reported by (1). It is also better than the results obtained by (18) where the success rate was only in 77% of subjects on the same therapy. The results in demonstrating that cabergoline's percentage reduction of serum prolactin levels is higher than bromocriptine is in agreement with the results obtained by other investigators who reported the superiority of cabergoline over bromocriptine in treating hyperprolactinaemic infertile women (1,28,11,3,30). It was unclear why cabergoline was more effective than bromocriptine in percentage reduction of serum prolactin levels but this greater efficacy might be explained by the fact that cabergoline had a higher affinity for dopamine receptor binding sites (28).

The results of this study revealed that there was decrease in pre-treatment progesterone levels of hyperprolactinaemic subjects. This finding was in agreement with the finding of other study where it was recorded that the serum level of progesterone was low in hyperprolactinaemic patients (1) Progesterone was low in hyperprolactinaemic patients because the production of progesterone from corpus luteum within the ovary could occur in luteal phase of the menstrual cycle. The production of progesterone is dependent on continued pituitary LH secretion. It is considered that hyperprolactinaemia is a cause of inadequate progesterone production during luteal phase because it is associated with luteal phase insufficiency and decrease pulsatile secretion of LH hormone (2,21). Elevated levels of prolactin was reported to decrease the life and action of the corpus luteum, thus decreasing progesterone production (11). Also higher concentration of prolactin caused decreased Follicle Stimulating Hormone-receptor binding and progesterone production. (8) revealed that infertile females had statistically lower progesterone level when compared to fertile females.

There was elevation of progesterone levels by both drugs. The mean difference of progesterone between the pre and post-treatment groups with bromocriptine was 9.16 ± 5.07ng/ml and with carbegoline it was 10.90 ± 4.96ng/ml as shown in table 4.5. The mean difference in the two drugs was statistically insignificant with p-value of 0.18. Progesterone level was < 2 ng/ml prior to ovulation and > 5 ng/ml after ovulation as stated by (26). Low progesterone during pregnancy can be one cause of recurrent miscarriages. Progesterone might had been responsible for creating a healthy environment in the womb by maintaining the uterine lining. It also reduced the chances of blood clots and the immune system responding to the feotus as if it was a foreign substance (25). A 2017 study published in the journal *Fertility and Sterility* found that for 59 women who'd experienced recurrent pregnancy loss (at least 2 previous losses), using vaginal micronized progesterone in their luteal phases prior to pregnancy carried healthy pregnancies (25).

The results of this study showed that both bromocriptine and carbegoline were equally good for progesterone elevation. These findings were supported by the study of (10) who stated that the dopamine agonist drugs have been reported to correct luteal phase defect associated with hyperprolactinaemia. As well as other study has observed that there was an inverse relationship between the serum level of prolactin and progesterone hormone in hyperprolactinaemia (2). The progesterone elevation recorded by subjects administered with bromocriptine and carbegoline was in conformity with the results by (9). It stated that: "A progesterone level over 5ng/ml probably indicated some form of ovulation but most medical practitioners would had expected a level over 10ng/ml on a natural cycle and a level over 15ng/ml on a medicated cycle". This showed that the drugs were equally effective for progesterone normalization- a level above 10ng/ml, which was considered proof of adequate ovulation. Also, in a study to show that high prolactin was linked to low progesterone and luteal phase defects, 33 luteal deficiency subjects with transient hyperprolactinaemia who were treated with bromocriptine to maintain mid-cycle prolactin levels between 5-15ng/ml had their integrated Luteinizing Hormone surge and their progesterone levels increased significantly during bromocriptine treatment (10).

Regarding the mean values of FSH and LH hormones, this study found significant increase in

post treatment subject's groups compared with the pre- treatment groups (tables 3 and 4). These results were in agreement with that recorded by (2), who reported the decrease in serum LH, FSH levels in hyperprolactinaemic women compared to normoprolactinemic women. The decrease in serum levels of FSH and LH hormones in hyperprolactinaemic infertile women was probably due to that high level of prolactin could work at both central and ovarian sites. In presence of high levels of prolactin, the ovulation might be suppressed due to the suppression of secretion of gonadotropins releasing hormone (GnRH) (6,14,23); because the high levels of prolactin interferes with hypothalamic-pituitary-gonadal axis through a positive feedback effect on dopamine secretion. Increase dopamine reduce GnRH secretion by suppressing arcuate nucleus function (2). This leads to reduction in pulsatile secretion of LH and FSH hormones. Also the high circulating levels of prolactin hormone interfering with the action of the gonadotrophins at the ovarian level and impairing normal gonadal steroid secretion, which in turn alters positive feedback effects at the hypothalamic and pituitary levels. This leads to lack of gonadotrophinscyclicity and to gonadal dysfuncation in women including amenorrhoea, oligomenorrhoea with anovulation or infertility (2,16,21). The significant elevation in FSH and LH levels observed in the post –treated subjects with both drugs appeared in close relation with the study by (2) who described that there was increase in serum FSH and LH during treatment with dopamine agonist drugs. On the other hand, (24) recorded higher levels of FSH, LH and prolactin among infertile women whose fasting state samples were collected during mid- cycle 14-16 day. (8), on a general note revealed that there was no difference in FSH and LH levels of infertile women when compared to fertile women.

However, the comparison of the elevation of FSH and LH effected by cabergoline or bromocriptine was not statistically siginificant (tables 5 and 6). In the case of FSH was in agreement with the report of (2) that there was no significant difference in serum FSH level in post treated patients with cabergoline drug compared with post treated patients with bromocriptine drug however for LH, it was not so.

It is worthy of note also, though for healthy subjects (72 healthy volunteers), (15), reported that single or multiple doses (up to 2 mg) of cabergoline resulted in selective inhibition of prolactin with no apparent effect on other anterior pituitary hormones (GH, FSH, LH, ACTH, and TSH) or cortisol.

Nevertheless, thepost treatment values of the parameters assayed fell within the internationally accepted standard reference ranges.

In this study, idiosyncratic reaction to bromocriptine was found in 3% of test subjects while none was recorded for the carbegoline group showing that it might be preferred in hyperprolactinaemic infertile women who reacted abnormally to bromocriptine. This result was in agreement with the reports of (16,2). A range of 5-18% of hyperprolactinaemic infertile females in Iraq had been reported to have been none reactive to bromocriptine treatment, with only partial lowering of plasma prolactin levels and an absence of tumor shrinkage (1).

There was evidence of higher number of pregnancy resumption with no loss to follow up with carbegoline therapy. Six subjects (16.6%) out of thirty-six who commenced for the carbegoline group became pregnant at completion of therapy while three out of thirty-six (8.3%) became pregnant at the completion of therapy for the bromocriptine group and were not included in the final analysis. The rate and ratio of pregnancy achievement recorded with carbegoline and bromocriptine was similar with the findings of (3) in their comparison of the drugs in the treatment of Sudanese infertile amenorrhic women in which pregnancy was achieved in 40% of women after treatment with bromocriptine and in 68% of the group under carbegoline treatment. On follow up hospital visits, for the carbegoline group all subjects came back for the post treatment test but six who were found to be pregnant were not included for the final study. They also adhered to treatment schedule. On the other hand, for the bromocriptine group, three subjects were lost to follow up. (3) also recorded good patient adherence by carbegoline group; stating that one of the advantages of treatment by carbegoline was the easy drug dose regimen administration since it was taken weekly with a low dose but bromocriptine was taken daily on high doses for a longer period. Carbegoline's dosing is less frequent and the drug is more tolerable, patient adherence may be better with cabergoline than with bromocriptine. (17).

The age category of hyperprolactinaemic infertile subjects mostly affected among the subjects of the two groups was 31-40years. It appeared to be in close association with the findings of (19) that recorded that the maximum infertile women population was found between the age group of 30-40 years. (2) stated that most common age group (28-32years) represented the highest percentage of total hyperprolactinaemic patients.

CONCLUSION

In conclusion, cabergoline and bromocriptine were confirmed to be effective in the treatment of hyperprolactinaemic infertile women in Orlu South East Nigeria because they effectively normalised the serum levels of **prolactin and elevated progesterone, FSH and LH of** hyperprolactinaemic infertile females who completed the medications. Cabergoline had the advantage over bromocriptine in higher percentage reduction of prolactin with no record of idiosyncratic reaction.

RECOMMENDATION

Hyperprolactinaemic infertile women who can afford carbegoline should not deny themselves access to carbegoline which brings the same effect with bromocriptine within a short duration of time or otherwise should use bromocriptine.

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