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Interplay between Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH) and Prolactin in Hyperprolactinaemic Infertile Women Treated with Cabergoline in Orlu, Nigeria

Ajaero, Oluchi Chinwe[1]; Offiah, Raymond Ogbonna[2]; Unekwe, Prince Chiazor[1]; Ajaero, Nnaemeka Uchendu[3]; Uzoma, Onyeka I.[4]

[1]Department of Pharmacology and Therapeutics, Nnamdi Azikiwe University, Awka, Nigeria
[2]Department of Pharmacology and Therapeutics, College of Medicine, Enugu State University of Science and Technology, Enugu, Nigeria
[3]Department of Medical Laboratory Science, Imo State College of Health and Management Sciences, Amaigbo, Nigeria
[4]Department of Obstetrics and Gynaecology, Imo State University Teaching Hospital, Orlu, Nigeria

ABSTRACT

The study evaluated the interplay between Follicle stimulating hormones, Leutenizing hormone, and prolactin in hyperprolactinaemic infertile female subjects treated with cabergoline in Orlu, South-East Nigeria. Hyperprolactinaemic females who were attending Gynaecology Clinic at Imo State University Teaching Hospital (IMSUTH) Orlu participated in the study. 30 hyperprolactinaemic females were administered 0.25mg cabergoline twice weekly for eight weeks. Serum prolactin, 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 and FSH in the pre and post treatment with cabergoline was determined by paired t-test. There was an inverse relationship between prolactin level and FSH and LH before and after treatment. Linear regression analysis showed that for every 0.14 and 0.02 unit change in the level of pretreatment prolactin, there is 1 unit change in FSH and LH level respectively. While for every 0.25 and 0.31 unit change in level of post treatment prolactin, there is 1 unit change in the level of FSH and LH respectively. Only change in post treatment LH following change in post treatment prolactin was statistically significant, and the P value < 0.05, however, others were not statistically significant.

KEYWORDS: *Infertility, Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Prolactin, Hyperprolactinaemia and Cabergoline*

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INTRODUCTION

Infertility is defined as the inability of a married couple to conceive after one year of regular unprotected sexual intercourse (22). Infertility can also refer to the biological inability of an individual to contribute to conception, or to a female who cannot carry a pregnancy to full term (4). Infertility is primary if the couples are unable to get pregnant, while secondary infertility is the inability to get pregnant after an earlier pregnancy (18). About 60 to 70 percent of all couples who try to conceive will succeed within six months. Another 20 percent will conceive within a year. When there is not always a medical condition that interferes with becoming pregnant, the remaining 10 to 20 percent of couples not conceiving after a year will have a higher risk of having a medical condition that interferes with conception (9).

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 (23). 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 (6).

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 (12). 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 (19).

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 (19).

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 (3). Hyperprolactinaemia can be associated with significant morbidity. It is characterized by the presence of high level of prolactin in the blood (5). 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 (11).

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 (8).

Cabergoline was developed during the 1980s. The most popular trade name for this agent is Dostinex, which is produced in the U.S. and many other countries by the giant pharmaceutical conglomerate Pharmacia (14). Cabergoline, ergot-derived dopamine agonist with a very long half-life, is an effective prolactin suppressor. It works by blocking prolactin secretion from the pituitary gland (24).

MATERIALS AND METHODS

Equipment and Sources

Prolactin, FSH and LH Accubind ELISA test kits from Monobind Incorporated, Lake Forest, CA92630, USA. 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 study evaluated the interplay between Follicle stimulating hormones, Leutenizing hormone, and prolactin in hyperprolactinaemic infertile female subjects treated with cabergoline 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, 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. 30 hyperprolactinaemic females were administered 0.25mg cabergoline twice weekly for eight weeks. Subjects 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, 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. Blood samples for the estimation of serum prolactin, luteinizing and follicle stimulating hormones were collected on day 2-3 of the women's cycle. 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 aged between 16 and 45 with hyperprolactinaemia with or without galactorrhoea.

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 36 women (test subjects) were recruited for the study. 12 out of the 36 women were students; 15 were government workers (health workers and teachers); 9 were self-employed. 83% (30 women) completed the study. 17% (6 women) did not complete the study due to pregnancy. Control subjects were 30 in number among which 15 were government workers, 10 were self-employed and 5 were students.

Biochemical Analysis

Serum prolactin, 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.

Table 1: Comparison of Prolactin, 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 ± 17.05	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 ± 1.31	4.0 ± 1.2	9.07	<0.001

SD = standard deviation.

Table 2: Levels of Prolactin, FSH and LH 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 ± 16.66	11.11 ± 3.54	12.37	<0.001
FSH (miu/ml)	3.34 ± 1.07	5.62 ± 1.74	12.04	<0.001
LH (miu/ml)	2.85 ± 1.05	5.22 ± 1.76	7.26	<0.001

SD = standard deviation.

Table 3: Bivariate Linear Regression Analysis of Prolactin and FSH or LH

	Unstandardised B	Standardised B	95% CI	P value
Pre-treatment				
Prolactin and FSH	-0.007	-0.142	-0.020-0.006	0.28
Prolactin and LH	-0.009	-0.203	-0.019-0.002	0.12
Post treatment				
Prolactin and FSH	-0.047	-0.252	-0.095-0.000	0.05
Prolactin and LH	-0.079	-0.311	-0.143- -0.016	0.02

Discussion

This study found that there was significant decrease in post treatment with cabergoline compared with pre-treatment groups regarding the mean values of serum prolactin hormone (tables 2). This result matches with the results got by (3) and (8) 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 (2; 6; 24; 20).

The data obtained from the present study revealed that cabergoline is effective in the treatment of hyperprolactinaemic infertility with regard to prolactin reduction. The current results are in agreement with several other studies reported over the years demonstrating the efficacy of cabergoline treatment in hyperprolactinaemia (1; 2; 5; 24). The percentage of reduction of serum prolactin level obtained in the present study by cabergoline is 79.30%. Cabergoline normalized prolactin levels in 100% of subjects. This is higher than that (87.7%) reported by (2). It is also better than the results obtained by (16) where the success rate was only in 77% of subjects on the same therapy.

Regarding the mean values of FSH and LH hormones, this study found significant increase in post treatment subjects compared with the pre-treatment groups (tables 2). These results were in agreement with that recorded by (3), who reported the decrease in serum LH, FSH levels in hyperprolactinaemic women compared to normoprolactinemic women. In presence of high levels of prolactin, the ovulation might be suppressed due to the suppression of secretion of gonadotropins releasing hormone (GnRH) (7; 13 and 20); 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 (3). 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 gonadotrophins cyclicity and to gonadal dysfuncation in women including amenorrhoea, oligomenorrhoea with anovulation or infertility (3; 15; 17). The significant elevation in FSH and LH levels observed in the post – treated subjects with cabergoline appeared in close relation with the study by (3) who described that there was increase in serum FSH and LH during treatment with dopamine agonist drugs. On the other hand, (21) recorded higher levels of FSH, LH and prolactin among infertile women whose fasting state samples were collected during mid- cycle 14-16 day. (10), on a general note revealed that there was no difference in FSH and LH levels of infertile women when compared to fertile women.

This study found that there was an inverse relationship between prolactin level and FSH and LH before and after treatment. Linear regression analysis showed that for every 0.14 and 0.02 unit change in the level of pretreatment prolactin, there is 1 unit change in FSH and LH level respectively. While for every 0.25 and 0.31 unit change in level of post treatment prolactin, there is 1 unit change in the level of FSH and LH respectively as shown in the table 3. Only change in post treatment LH following change in post treatment prolactin was statistically significant, and the P value < 0.05, however, others were not statistically significant.

CONCLUSION

In conclusion, cabergoline confirmed to be effective in the treatment of hyperprolactinaemic infertile women in Orlu South East Nigeria because it effectively normalised the serum levels of prolactin and elevated FSH and LH of hyperprolactinaemic infertile females who completed the medications. The levels of prolactin in hyperprolactinaemic infertile female subjects did not affect follicle stimulating

hormone (FSH) and luteinizing hormone (LH) significantly after treatment.

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