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Research Article

Levels of prolactin, progesterone, estradiol, luteinizing hormone and follicle stimulating hormone in infertile women in Calabar, Nigeria

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ABSTRACT

Background: Infertility is defined as the inability of a couple to achieve conception despite frequent unprotected, well timed sexual intercourse for one year duration. Therefore the aim of our study was to estimate the levels of progesterone, estradiol, luteinizing hormone, follicle stimulating hormone in infertile women.
Methods: One hundred and two (102) volunteers infertile women; aged 20-45 years were recruited from the University of Calabar Teaching Hospital. They were further divided into three groups based on their prolactin levels; namely those with normal ovarian hormones value (normal); (n=32), those with prolactin values between 25 – 60ng/ml (moderate) (n=46) and those with prolactin values >60ng/ml (high); (n=24). Sixty (60) apparently healthy, age matched women were also selected to serve as the control group. Sera samples were obtained from the subjects and the following parameters were measured using DRG Enzyme Linked Immunosorbent Assay; prolactin, progesterone, estradiol (E2), follicle stimulating hormone (FSH) and luteinizing hormone (LH).
Results: In this study, the prolactin and E2 values were significantly ($p<0.05$) higher in the high group compared to the normal ovarian profile and moderate group, while progesterone levels were significantly higher in the normal group compared to the moderate and high groups. There was no significant difference in the values of LH and FSH among the groups ($p>0.05$). There was a positive correlation between E2 and prolactin, progesterone and FSH ($r=0.239$; 0.368 and 0.217 respectively, $p<0.05$) and a strong positive correlation between FSH and LH ($r=0.677$) in the infertile women.
Conclusions: There was a positive correlation between E2 and progesterone with reduced concentration of FSH in women with normal, moderate and high prolactin concentrations. Therefore, there is need for anti-oxidant therapy or supplements for these subjects.

Keywords: Progesterone, Estradiol, Luteinizing hormone, Follicle stimulating hormone, Infertile women

INTRODUCTION

Infertility is defined as the inability of a couple to achieve conception despite frequent unprotected, well timed sexual intercourse for one year duration. It also includes the inability of a woman to carry a pregnancy to the delivery of a live baby.[1] Infertility occurs in one out of five couple of reproductive age and in ten to twenty per cent of these cases, there seems to be no definitive cause, therefore these are classified as unexplained infertility.[2,3]

Studies by Boivin et al. found that the prevalence of infertility was nine per cent, for less developed countries.[4] In Britain male factor infection accounts for 25% of infertile couple while 25% remain unexplained and 50% are female cause with 25% being due to anovulation and 25% tubal problem/others.[5] In Africa, infertility is a major reproductive health problem with regional prevalence rates of 30-40%.[6] Adetoro and Ebomoyi reported infertility prevalence of 30.3% among women living in Nigeria.[7] A retrospective study done by Ekwere et al. on patients coming to the Obstetrics and

Gynecology clinic in Calabar, the causes of infertility was 58% female, 30% male while 12% were both causes.[8] Primary infertility was found in 69.7% of the males and 34.5% of the female, while secondary infertility was30.3% in males and 65.5% in females; Infection being the strongest predisposing factor. The WHO defines health as "a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity.[9] Infertility, accordingly, is a source of diminished health and social well-being. Therefore there is need to estimate the levels of progesterone, estradiol, luteinizing hormone, follicle stimulating hormone in infertile women.

METHODS

A group of women attending the infertility clinic in the Department of Obstetrics and Gynecology and coming for infertility test in the Department of Chemical Pathology of the University of Calabar Teaching Hospital (UCTH) were selected for the study. The selection of patients was done with the help of a Gynaecologist in the Obstetrics and Gynecology Department of the hospital. One hundred and two (102) volunteers infertile women, aged 20-45 years were recruited. Sixty (60) apparently healthy, age matched women who had given birth to at least one child within the last three years, were selected to serve as the control group. Approval was given from the Health Research Ethical Committee (HREC) of the Hospital and the subjects all gave informed consent to participate in the study. Their confidentiality was maintained.Inclusion criteria used was that apparently healthy women with infertility problems and healthy women who had given birth to at least one child within the last three years whilewomen who were pregnant or older than 45 years of age and those with high blood pressure and diabetes were excluded.

Five milliliters (5 ml) of venous blood was obtained from these test subjects in the luteal phase (21^{st} – 23^{rd} day) of their menstrual cycle into clean plain bottles (containing no anticoagulants). The blood was allowed to clot and was centrifuged at 3000 rpm for five (5) minutes. The serum was then separated by the use of pasteur pipettes into serum containers with tight screw caps and was stored at -20^0C in aliquots of one milliliter until ready for use. The sample was used for prolactin, progesterone, estradiol, follicle stimulating hormone (FSH) and luteinizing hormone (LH) assays using DRG Enzyme immunosorbent assay.

Data analysis

The data was analysed using Microsoft Excel and PASW (Predictive Analysis Software) version 18 packages from SPSS Inc. USA.

RESULTS

Their mean ages where 31.1±5.37 yrs and 33.1±4.91 yrs respectively. The infertile women were further divided into three groups based on their prolactin levels; namely those with normal ovarian hormones value (normal); (n=32), those with prolactin values between 25 – 60ng/ml (moderate) (n=46) and those with prolactin values greater than 60ng/ml (high); (n=24). Table 1 shows the comparison of prolactin, progesterone, luteinizing hormone (LH), Follicle Stimulating Hormone (FSH) and estradiol (E2), between infertile women groups of normal ovarian profile, moderate and high prolactin. Here, the prolactin and E2 values were significantly higher in the high group compared to the normal ovarian profile and moderate group while progesterone levels were significantly higher in the normal group compared to the moderate and high groups. There was no significant difference in the values of LH and FSH among the groups ($p>0.05$).Figure 1 shows the correlation graph of E2 against prolactin in the test group. There was a positive correlation. ($r=0.239$; $p<0.05$). Figure 2 shows the correlation graph of LH against progesterone in the control group. There was a negative correlation. ($r= -0.263$; $p<0.05$).while the correlation graph of E2 against progesterone in the test group was a positive correlation. ($r=0.368$; $p<0.05$) in Figure 3. Figure 4 shows the correlation graph of FSH against LH in the test group. There was a positive correlation ($r=0.677$; $p<0.05$).

Table 1: Comparison of prolactin, progesterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol (E2) among the infertile women groups.

Group parameter	Normal prolactin	Moderate prolactin	High prolactin	Calc "f"	Crit "f"	P-value
Prolactin(ng/ml)	15.5±4.86	35.7±9.98	104.4±26.68	267.2	3.088	p<0.05
Progesterone(ng/ml)	15.9±6.16γ#	10.37±5.18	11.88±7.07	8.377	3.088	p<0.05
LH (µIU/ml)	12.9±16.39	10.1±13.96	5.42±4.18	2.201	3.088	p>0.05
FSH (µIU/ml)	7.32±9.60	5.75±9.51	3.1±1.57	1.700	3.088	p>0.05
E_2 (pg/ml)	89.9±39.33	78.9±31.86	103.1±47.74#	3.199	3.088	p<0.05
N	32	46	24			

Mean ± SD; * significantly higher than normal group; # significantly higher than moderate group; γ significantly higher than high group

The correlation graph of E2 against FSH in the test group was a positive correlation in Figure 5 (r=0.217; p<0.05).

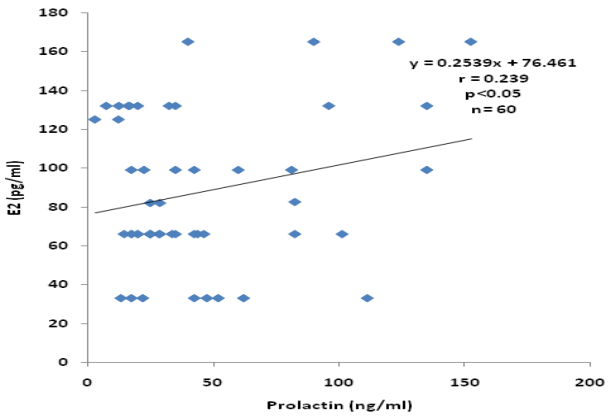

Figure 1: Correlation graph of E2 against prolactin in the test group. There was a positive correlation (r = 0.239; p<0.05).

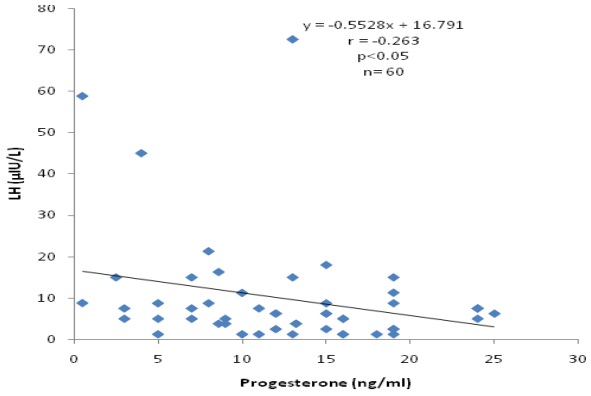

Figure 2: Correlation graph of LH against progesterone in the test group. There was a negative correlation (r = -0.263; p<0.05).

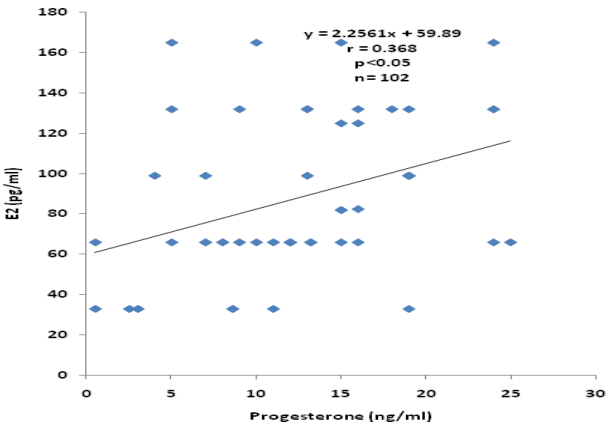

Figure 3: Correlation graph of E2 against progesterone in the test group. There was a positive correlation (r = 0.368; p<0.05).

DISCUSSION

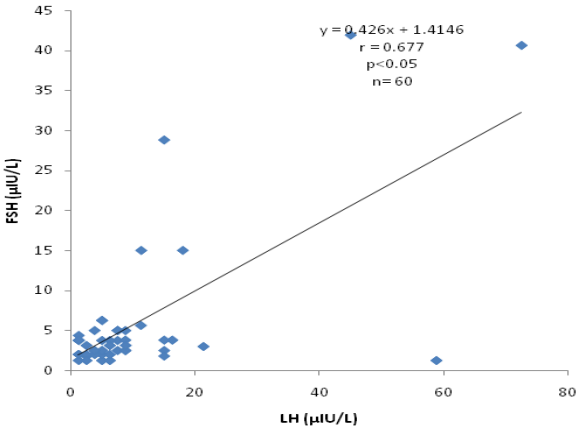

Figure 4: Correlation graph of FSH against LH in the test group. There was a positive correlation (r = 0.677; p<0.05).

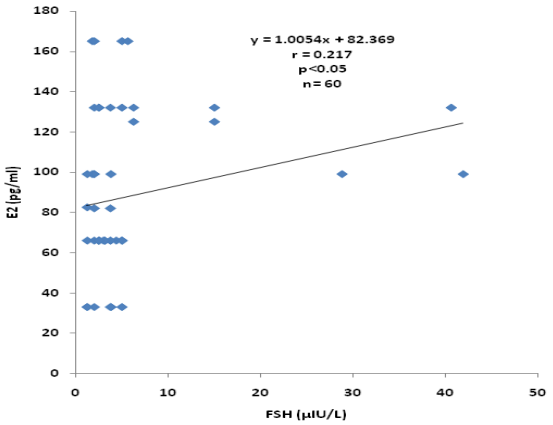

Figure 5: Correlation graph of E2 against FSH in the test group. There was a positive correlation (r = 0.217; p<0.05).

This study was conducted to determine and compare prolactin, progesterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol (E2), in fertile and infertile women. Glutathione peroxidase (GPx) activity is high in corpus luteum. Glutathione peroxidase activity is secreted from human epididymal cells in a region dependent manner and is regulated by androgens.[10] It enhances steroid hormone synthesis and it also causes developing follicles to increase in the activity of cytochrome P450, which in turn generates ROS such as hydrogen peroxide (H_2O_2).[11,12] Behl and Pandey observed that catalase and estradiol activity in ovarian follicles fluctuated with FSH.[13] Catalase activity and E_2 release were greater in large follicles than in medium or small follicles. Since the dominant follicle will be the follicle with the highest estrogen concentration, the concomitant increases in catalase and E_2 in response to FSH suggest a role for catalase in follicular selection and prevention of apoptosis.[13]

A positive correlation between estrogen and prolactin was observed in infertile subjects. Usually estradiol-induced prolactin surge accompanies the LH surge in several species, including sheep. However, the neural mechanisms underlying this surge remain poorly understood. Skinner and Caraty, observed that the generation of the prolactin surge is not dependent on the co-secretion of a prolactin-releasing peptide in the hypophyseal portal blood or cerebrospinal fluid.[14] The neuronal pathways targeted by estradiol and progesterone to modulate prolactin secretion at the time of the LH surge remains to be identified.

The study showed a negative correlation between luteinizing hormone and progesterone in infertile women. Usually, once a follicle has been stimulated, estradiol production causes that specific follicle to be more receptive to effects from FSH. After ovulation, LH is suppressed by progesterone and estradiol. But the effect of LH on the corpus luteum function is increased.[15,16]

The hormones, estrogen and progesterone were positively correlated in the infertile subjects. Estrogen levels rise and fall twice during the menstrual cycle. Estrogen levels rise during the mid-follicular phase and then drop precipitously after ovulation. This is followed by a secondary rise in estrogen levels during the mid-luteal phase with a decrease at the end of the menstrual cycle. The secondary rise in estradiol parallels the rise of serum progesterone and 17α-hydroxyprogesterone levels. Ovarian vein studies confirm that the corpus luteum is the site of steroid production during the luteal phase.[17] Estradiol is essential for the development of proliferative endometrium and is synergistic with progesterone for the development of the changes in the endometrium that initiates shedding.[18]

A positive correlation between follicle stimulating hormone (FSH) and luteinizing hormone (LH) was observed in the infertile subjects. Usually a few days before day 1 of the cycle, FSH shows a slight but important peak probably triggered by a fall in estradiol level that briefly eliminates the negative feedback effect. This peak of FSH begins the growth and maturation of a receptive ovarian follicle. Follicle stimulating hormone level falls again and remains fairly low through the follicular phase owing to negative feedback from estradiol produced by the developing follicle. However the effect of FSH, aided by estradiol, acts on the cells of the follicle to increase responsiveness of LH receptors by the time of the mid cycle surge. Follicle stimulating hormone and LH receptors are increased either in their number or in their affinity for corresponding gonadotropin or in both.[16,19] The LH surge stimulates luteinization of the granulosa cells and stimulates the synthesis of progesterone responsible for the mid cycle FSH surge.[20] Estradiol levels fall dramatically immediately prior to the LH peak. This may be due to LH down regulation of its own receptor or because of direct inhibition of estradiol synthesis by progesterone. Progesterone is also responsible for stimulating the mid cycle rise in FSH. Elevated FSH levels at this time are thought to free the oocyte from follicular attachments, stimulate plasminogen activator, and increase granulosa cell LH receptors. The mechanism causing the postovulatory fall in LH is unknown. The decline in LH may be due to the loss of the positive feedback effect of estrogen, due to the increasing inhibitory feedback effect of progesterone, or due to a depletion of LH content of the pituitary from down regulation of GnRH receptors.[21]

The study showed a positive correlation between estrogen and follicle stimulating hormone in the infertile subjects. There appears to be a two separate feedback centers in the hypothalamus- a tonic negative feedback center in the basal medial hypothalamus and a cyclic positive feedback center in the anterior lobe of the hypothalamus. Low levels of estradiol such as those which are present during the follicular phase, affect the negative feedback center, whereas, high levels of estradiol, such as seen just before the mid cycle LH peak, trigger the positive feedback center. Progesterone in combination with estrogen affects the negative feedback center in the luteal phase.[16] Estradiol enhances the FSH effect on a ripening follicle through changes in FSH receptors of the follicular cells but suppresses pituitary FSH and LH release during the follicular phase through the negative feedback. As estradiol production increases near the mid cycle, the effect on the positive feedback center takes over, with increased release of GnRH from the hypothalamus leading to increased release of LH and FSH from the anterior lobe of the pituitary gland.[15,19]

CONCLUSION

There was a positive correlation between E2 and progesterone with decreased value of FSH in women with normal, moderate and high prolactin levels which is expected. However, the FSH values for the three groups were not significantly different from each other. The decrease in progesterone leads to an increase in LH as a negative feedback mechanism. However, the E2 and progesterone have a relationship which is expected in infertile women. An increase in LH is normally accompanied with an increase in FSH in normal women; same is seen even with the infertile women. Furthermore, the thyroid status of infertile women should also be assessed to ascertain the role of hypothyroidism in hyperprolactinemic infertile women.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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