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RESEARCH ARTICLE OPEN ACCESS

Serum prolactin levels and its clinical correlates in women presenting with infertility at the gynaecologic clinic of a tertiary hospital in North-central Nigeria

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Abstract
Objectives: We aimed to determine and compare the serum prolactin levels in infertile women and fertile controls and to compare the clinical presentations such as menstrual disorders, and visual field defects to prolactin levels in both groups.
Methods: A comparative descriptive cross-sectional study involving reproductive-aged women with infertility Consenting female hospital staff in the same age group, without prior infertility were the control group. All participants were examined and had serum prolactin assay. The data was analyzed using the SPSS version 21. Probability (*p*) values less than 0.05 were accepted as statistically significant.
Results: The mean ages were 33.11 ± 5.62 years (subject) and 32.92 ± 4.82 years (controls). Hyperprolactinaemia was recorded in 56.6% and 22.6% of infertile women and controls, respectively. The Mean serum prolactin value of 24.93 ± 16.51ng/ml in the subjects was higher than 17.15 ± 8.05ng/ml in the controls (*p*-value =0.003). Median serum prolactin values of infertile subjects with milky nipple discharge, decreased libido and galactorrhoea were significantly higher than that of fertile controls (*p* value= 0.001, 0.033 and 0.016 respectively). Comparison of amenorrhoea, galactorrhoea and abdominopelvic mass were significantly related to hyperprolactinaemia in infertile subjects than in fertile controls (*p*-value = 0.040, 0.014 and 0.040 respectively).
Conclusion: Serum prolactin levels of infertile women attending the gynaecologic clinic in UITH were significantly higher than fertile controls. Prevalence of hyperprolactinaemia was higher among the infertile subjects and clinical features were more demonstrable in fertile controls than infertile subjects.

Keywords: Serum prolactin levels, Infertility, Hyperprolactinaemia, Galactorrhoea

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Plain English Summary
The research was carried out at the Department of Obstetrics and Gynaecology, University of Ilorin Teaching Hospital. It involves checking for the blood level of a hormone called prolactin in women between the ages of 15 and 45 years. A total of 106 women who agreed to participate in the research were recruited and this comprised 53 each of women who had infertility and those presumed to be fertile. The participants were asked to fill out a questionnaire comprising information such as their biodata, gynaecology history, presence of milky discharge, excessive hair growth, etc. Also, an examination was carried out which included a breast examination, abdominal examination and eye examination. Blood samples were taken from the women to check the prolactin level in it.
All information obtained was analyzed using computer software and results were displayed in tables and charts. It was discovered that blood prolactin levels of infertile women attending the gynaecologic clinic in UITH were significantly higher than fertile women. Also, the occurrence of elevated blood levels of prolactin and clinical features were more demonstrable in subjects than in controls.

Introduction
Childbearing is revered in all societies; thus, infertility remains a source of pain, anxiety and shame to affected couples (1). Although infertility is a global problem, its incidence and prevalence vary across populations. Infertility constitutes a major reason for gynaecologic consultation (2, 3) and affects 15% of couples attempting their first pregnancy, in which case it is called primary infertility; while those with secondary infertility are about 10% of the population (4). The World Health Organization (WHO) estimated that 15% of couples around the world experience problems in conception (5). The consequences of childlessness in developing countries are numerous and far-reaching on the woman, ranging from social, and economic to psychological (6, 7, 8, 9).
In the developed nations, female infertility is majorly from endometriosis, anovulation from polycystic ovarian disease and hyperprolactinaemia with or without galactorrhoea (10). Some of the associated factors found in the developed country are now being increasingly recorded in developing countries (9, 11) and becoming important causes of female infertility in some reports from Nigeria (6, 12).
Tubal factor has been extensively researched because of the predominant role it plays in infertility in sub-Saharan Africa (9, 12), as a result of recurrent risks from pelvic inflammatory disease (PID), sexually transmitted diseases (STDs), post-abortal and puerperal infections which are common in sub-Saharan Africa (9, 10, 12).
Ovulatory factors have now emerged as an important cause of infertility in sub-Saharan Africa with anovulation accounting for 15-23.8% of infertility (2, 9, 12, 13). According to the WHO classification of ovulatory disorders, hyperprolactinaemic anovulation (class 1V) accounts for 5-10% of anovulatory disorders in women (13).
Prolactin assay is usually included in the differential workup for female patients who present with amenorrhoea, oligomenorrhoea, galactorrhoea, or infertility (6, 14, 15, 16). Prolactin is a polypeptide hormone, secreted in a pulsatile manner from the anterior pituitary gland (6, 17). It enlarges the breasts in preparation for breastfeeding and induces lactation (6, 18). Emokpae et al, in their previous report on infertile women, observed that a significant proportion of the subjects were observed to have high prolactin levels (19). Hyperprolactinaemia may be caused by a variety of conditions, such as sleep, stress, sexual stimulation, and trauma (6), it can also result from hormonal imbalance, chronic medical conditions, drugs and tumours as well as idiopathy (20). It may be associated with a variety of menstrual cycle disturbances including oligo-ovulation, corpus luteum insufficiency and amenorrhea (21, 22).
Hyperprolactinaemia adversely affects the reproductive cycle in females by inhibiting the normal luteinizing hormone (LH) surge that stimulates ovulation resulting in infertility (14, 21, 22). In males, high levels of serum prolactin have been associated with, infertility, hypogonadism, galactorrhoea, decreased libido and potency (4, 22). It can also be associated with osteopaenia, recurrent headaches, visual field defects and other symptoms suggestive of space-occupying lesions (23).
In Nigeria, there are limited studies done to elucidate the other accompanying symptoms in infertile women with deranged prolactin levels. This study seeks to determine the level of prolactin, the menstrual pattern and other symptoms associated with deranged prolactin levels in infertile women and compare this with levels in fertile controls.

Materials and Methods
Study site
The study was carried out in the gynaecology clinics of the Department of Obstetrics and

Gynaecology of the University of Ilorin Teaching Hospital, Ilorin, Kwara State, Nigeria. The University of Ilorin Teaching Hospital is located at Oke-Oyi, Old Jebba Road in Ilorin. It predominantly plays the role of a teaching hospital but equally offers primary and secondary health services. It serves as a major referral centre for Kwara State and parts of the nearby states of Oyo, Osun, Ekiti, Kogi and Niger states. The gynaecology clinic is open to all and not limited to referred cases, an average of about 144 women access healthcare at the gynecologic clinics weekly, with 25% of them being for infertility cases (follow-up and new cases).

Study Population
Women of the reproductive age group (15 to 45 years) who presented to the University of Ilorin Teaching Hospital, with a history of inability to conceive for one year or more were studied. The control group comprised consenting fertile women matched for age, within the hospital community. They were non-lactating and non-pregnant women who had a pregnancy carried to term irrespective of the outcome within two years before recruitment for the study.

Eligibility criteria
Consenting women of reproductive age group (18 to 45 years) with infertility (primary or secondary), with or without menstrual irregularities. Consenting fertile women matched for age within the hospital community that has carried a pregnancy to term irrespective of the outcome within two years before recruitment into the study and also non-lactating women who had stopped all forms of breastfeeding for at least 6 months before recruitment into the study.
Refusal of the patient to participate, those with the established cause of infertility i.e. the non-hormonal cause of infertility, women younger than 18 years or older than 45 years of age, patients with the use of drugs that alter prolactin production e.g bromocryptine, cabergoline, L- dopa, cimetidine, chlorpromazine, reserpine, Methyl dopa and phenothiazines within six months before recruitment and those who had any form of physical exercise or a chest wall massage within 24 hours before recruitment. Sexual intercourse within 24hrs, epileptic seizure patients.

Study Design
The study was a comparative descriptive cross-sectional study of women of reproductive age group with a history suggestive of infertility, who met the criteria and those of fertile controls.

Sample Size Determination
The sample size was determined by the formula (24). Using a previous study by Salah Eldin et al (23), a minimum sample size of 106 was calculated i.e. 53 subjects in each arm of the study.

$$n = \frac{(u + v)^2 (\sigma_1^2 + \sigma_0^2)}{(\mu_1 - \mu_0)^2}$$

Sampling Technique
A purposive sampling method was used in which fertile subjects and infertile controls were recruited consecutively till the sample size was complete.

Visual Field Assessment
The visual field of each participant was assessed using a visual field analyser. AP-125 automatic visual field plotter made by Kowa Company Limited, Tokyo, Japan. All participants were assessed at the ophthalmology clinic with the assistance of the hospital optometrist. The optometrist assisted in assessing the visual acuity and the central visual field. The findings were presented to an ophthalmologist who reviewed the findings and thereafter recommended further evaluations and treatments for those with abnormal results. Bitemporal hemianopia was the abnormality of interest as this is described as the visual field defect associated with pituitary adenomas and prolactinomas due to its compression of the optic chiasma.

Breast Examination
The breast examination aimed to demonstrate galactorrhoea. The consenting participants were asked to sit down and lean forward, with the chest properly exposed the breasts were examined one after the other. The breast was inspected for any discharge or abnormalities. The hand was placed farther from the areola close to the base of the breast and was firmly and gently palpated towards the nipple in all four quadrants. The nipple was then inspected for the presence of fluid on the nipple. A female chaperone, who had been trained on the proper conduct of breast examination before the study was present at the examination of all participants. Those with galactorrhoea were handed over to the managing units for further evaluation and treatment.

Blood Sample Collection for Serum Prolactin Estimation
The blood sample was taken in the morning before the breast examination was done, so as not to alter the results due to breast examination at

recruitment. A suitable site was chosen, and a tourniquet was applied. Disposable gloves were worn and the site for venepuncture was disinfected with 70% alcohol. Then, 5ml of venous blood was withdrawn, the tourniquet was removed and dry gauze was placed on the needlepoint and held in place for about 20 seconds to ensure haemostasis. The blood sample was put into a clean plain bottle to allow the sample to clot and obtain the serum required for the test. The sample was then transported to the laboratory immediately after collection in batches for analysis using the Prolactin Hormone (PRL) Test System (25).

Data collection

The recruitment of patients was at the gynaecology clinics of the hospital, as this is the point of presentation of patients seeking care for gynaecological conditions, while that of controls was from the different departments and sections of the hospital. Eligible women who satisfied the inclusion criteria were informed and counselled about the study in a language they could understand and informed consent was obtained. A study proforma, designed to obtain socio-demographic status, menstrual pattern, history of galactorrhoea, history of infertility and other symptoms suggested to be associated with elevated prolactin level was administered. Thereafter, a physical examination was performed; this included the height and weight (with calculation of the body mass index), neck, breast and abdominal examinations, and the results were recorded. The visual field assessment of all participants was done and blood samples were collected for prolactin assay. Normal range of serum prolactin used for the study was 1.2-19.5ng/ml and a value above the normal range is hyperprolactinemia (> 19.5ng/ml) while a value below is hypoprolactinemia (< 1.2ng/ml). 1.0ng is equivalent to 21.2 mIU/ml.

Data Analysis

The data was analyzed using the Statistical Package for Social Sciences software (SPSS) version 21. The results were presented in tables. Continuous variables that were normally distributed were presented as means with standard deviation and analyzed using student's t-test, while those that were not normally distributed were presented as median with interquartile range and analyzed using Mann Whitney U test. Categorical variables were presented as proportions and analyzed using the Chi-square test. Increased risk of high prolactin within the study groups was determined using Odds ratio with 95% confidence interval and the variables that show significant relationship at univariate analysis were used to determine the predictor of elevated serum prolactin at multivariate level using binary logistic regression analysis. Probability (*p*) values less than 0.05 were accepted as statistically significant.

Results

A total of one hundred and six (106) women were enrolled on the study from January to July 2017. This comprised fifty-three infertile patients attending gynaecology clinics in the University of Ilorin Teaching Hospital and fifty-three fertile controls.

Sociodemographic Variables, Parity and Anthropometric Parameters

Table 1 shows sociodemographic variables, parity and anthropometric parameters of the infertile women and controls. The mean age for the infertile subjects was 33.11 ± 5.62 years while the mean age for the control group was 32.92 ± 4.82 years. None of the participants was less than 18 years old. There was a statistically significant relationship between the parity of infertile and fertile control with a p-value of < 0.001. Other variables showed no significant relationship between both groups except for occupation with a p-value of <0.001.

Table 1: Socio-demographic variables, parity and anthropometric parameters of the infertile women and the controls

Sociodemographic variable	Infertile women n (%)	Control n (%)	Total n (%)	χ^2	*p*-value
Age group (years)					
<25	2 (3.8)	2 (3.8)	4 (3.8)	0.069	0.999
25 – 29	15 (28.3)	15 (28.3)	30 (28.3)		
30 – 34	14 (26.4)	13 (24.5)	27 (25.5)		
35 – 39	15 (28.3)	16 (30.2)	31 (29.2)		
40 – 45	7 (13.2)	7 (13.2)	14 (13.2)		
Mean ± SD	33.11 ± 5.62	32.92 ± 4.82		0.186	0.853
Range	23 – 45	24 – 43			
Occupation					

Artisan	2 (3.8)	0 (0)	2 (1.9)	62.043	<**0.001***
Civil Servant	6 (11.3)	42 (79.2)	48 (45.3)		
Trade/Business	27 (50.9)	0 (0)	27 (25.5)		
Dependant	6 (11.3)	0 (0)	6 (5.7)		
Others	12 (22.6)	11 (20.8)	23 (21.7)		
Education					
None	1 (1.9)	1 (1.9)	2 (1.9)	5.571	0.134
Primary	6 (11.3)	1 (1.9)	7 (6.6)		
Secondary	10 (18.9)	6 (11.3)	16 (15.1)		
Others	36 (67.9)	45 (84.9)	81 (76.4)		
Ethnicity					
Yoruba	49 (92.5)	50 (94.3)	99 (93.4)	2.343	0.673
Nupe	1 (1.9)	0 (0)	1 (0.9)		
Fulani	0 (0)	1 (1.9)	1 (0.9)		
Igbo	2 (3.8)	1 (1.9)	3 (2.8)		
Others	1 (1.9)	1 (1.9)	2 (1.9)		
Parity					
0	31 (58.5)	0 (0.0)	31 (29.2)	44.335	<**0.001***
1	11 (20.8)	23 (43.4)	34 (32.1)		
2 – 4	11 (20.8)	29 (54.7)	40 (37.7)		
> 4	0 (0.0)	1 (1.9)	1 (0.9)		
Weight (kg)					
Mean ± SD	65.55 ± 16.38	65.79 ± 12.66		-0.083^{t}	0.934
Height (m)					
Mean ± SD	1.59 ± 0.11	1.62 ± 0.06		-1.823^{t}	0.071
BMI (kg m^{-2})					
Mean ± SD	26.05 ± 5.98	24.98 ± 4.68		1.007^{t}	0.316

χ^2: Chi square test; t: Independent Samples T test; *: *p* value < 0.05 (statistically significant)

Serum Prolactin Levels of Infertile Women and Fertile Controls

Table 2 shows that 56.6% of the infertile women had high serum prolactin levels compared with 22.6% of controls. There was no record of values lower than the normal range (1.2- 19.5ng/ml) in both groups. The infertile women were 4.457 times more prone to hyperprolactinaemia than the fertile controls (p-value = 0.001). The mean was 24.93 ± 16.51ng/ml in the infertile and 17.15 ± 8.05ng/ml in the control group, this difference was statistically significant (*p*-value = 0.003).

Table 2: Serum Prolactin levels of infertile Subjects and Fertile Controls

Prolactin (ng/ml)	**Infertile women n (%)**	**Control n (%)**	**Total N (%)**	**OR (95% CI)**	**Test statistic**	***p*-value**
High	30 (56.6)	12 (22.6)	42 (39.6)	4.457(1.92-10.34)	12.777$^{\chi 2}$	**<0.001***
Normal	23 (43.4)	41 (77.4)	64 (60.4)			
Total	**53 (100)**	**53 (100)**	**106 (100)**			
Mean ± SD (ng/ml)	24.93 ± 16.51	17.15 ± 8.05			3.085^{t}	**0.003***
Range (ng/ml)	12 – 90	7 – 55				

χ^2: Chi-square test; OR (95% CI): Odds ratio at 95% confidence interval; *: *p*-value < 0.05 (statistically significant); t: Independent Samples T-test. Reference range of serum prolactin: 1.2-19.5ng/ml

Comparison of Clinical Presentations Related to Prolactin Levels in Subject and Controls

Table 3 shows the comparison of median serum prolactin values of the symptomatic subjects and symptomatic controls. The median serum prolactin value of infertile women with a history of milky nipple discharge and decreased libido were 23.0ng/ml and 23.20ng/ml respectively, when compared with 16.0ng/ml and 16.75ng/ml in fertile controls with the same symptoms, these were significant with *p* value=0.001 and 0.033 respectively**.** Hence, milky nipple discharge and decreased libido in infertile women were related to hyperprolactinaemia. The median serum prolactin

levels of infertile women when compared with the fertile group for other symptoms were not statistically significant. The median serum prolactin level of infertile women, who had galactorrhoea demonstrable, was 20.50ng/ml and this was significantly higher than the median serum prolactin level of 16.50ng/ml in fertile controls, *p*-value = 0.016. Other examination findings had no statistically significant correlation.

Table 3: Comparison of serum prolactin levels in symptomatic subjects and symptomatic controls

Clinical Features	Prolactin level (ng/ml) Infertile Women Median (IQR)	Fertile Control Median (IQR)	U	*p* value
Symptoms				
Milky nipple discharge	23.00 (20.00 – 34.50)	16.00 (13.88 – 19.63)	46.500	**0.001***
Headache	20.00 (15.75 – 32.00)	16.50 (12.00 – 25.75)	42.000	0.292
Blurring of vision	44.75 (18.88 – 79.25)	26.50 (20.75 – 31.50)	8.000	0.730
Previous miscarriage	20.00 (14.50 – 26.50)	16.50 (12.25 – 19.50)	61.000	0.098
Cold intolerance	21.25 (17.50 – 36.38)			
Weight gain	20.25 (19.25 – 28.50)	17.00 (11.75 – 23.25)	33.500	0.062
Decreased libido	23.20 (20.00 – 38.00)	16.75 (14.75 – 23.63)	27.000	**0.033***
Cessation of menses	22.50 (17.38 – 45.25)			
Intermenstrual bleeding	20.00 (16.00 – 39.25)			
Examination findings				
Facial hair	26.50 (21.65 – 48.38)	22.25 (15.38 – 26.88)	10.000	0.197
Acne	52.00 (25.50 – 84.88)			
Visual field	20.00 (15.00 – 23.13)	14.50 (12.25 – 19.75)	25.000	0.073
Galactorrhoea	20.50 (15.50 – 34.50)	16.50 (13.38 – 19.63)	118.500	**0.016***
Abdominal mass	21.00 (17.50 – 32.25)			

U: Mann-Whitney U test; *: *p* value < 0.05 (statistically significant)

Table 4 shows the comparison of symptoms in subjects and controls with high prolactin values. Study participants that had cessation of menses were 33.3% of subjects and none among the controls. This comparison was statistically significant, *p* value= 0.040. other symptoms showed no significant relationship between both groups.

Table 4: Comparison of Symptoms in subjects and controls with hyperprolactinemia

Symptoms	High Prolactin Subjects n = 30(%)	Control n =12 (%)	OR (95% CI)	χ^2	*p*-value
Milky nipple discharge					
Yes	16 (53.3)	3 (25.0)	3.429 (0.772 – 15.222)	2.778	0.096
No	14 (46.7)	9 (75.0)			
Headache					
Yes	7 (23.3)	4 (33.3)	0.609 (0.140 – 2.643)	0.443	0.505
No	23 (76.7)	8 (66.7)			
Blurring of vision					
Yes	3 (10.0)	4 (33.3)	0.222 (0.041 – 1.207)	3.360	0.067
No	27 (90.0)	8 (66.7)			
Previous miscarriage					
Yes	8 (26.7)	2 (16.7)	1.818 (0.325 – 10.157)	0.473	0.492
No	22 (73.3)	10 (83.3)			
Cold intolerance					
Yes	3 (10.0)	0 (0.0)	NA	1.292	0.545
No	27 (90.0)	12 (100.0)			
Weight gain					
Yes	10 (33.3)	3 (25.0)	1.500 (0.331 – 6.798)	0.279	0.598
No	20 (66.7)	9 (75.0)			
Decreased libido					

Yes	12 (40.0)	2 (16.7)	3.333 (0.618 – 17.970)	2.100	0.277
No	18 (60.0)	10 (83.3)			
Cessation of menses					
Yes	10 (33.3)	0 (0.0)	NA	5.250	**0.040***
No	20 (66.7)	12 (100.0)			
Intermenstrual bleeding					
Yes	3 (10.0)	0 (0.0)	NA	1.292	0.545
No	27 (90.0)	12 (100.0)			

χ^2: Chi-square test; *: *p*-value < 0.05 (statistically significant); OR (95% CI): Odds ratio at 95% confidence interval

Table 5 shows the comparison of examination findings in subjects and controls with high prolactin values. Galactorrhoea was demonstrable in 66.7% and 25% of infertile subjects and fertile controls with hyperprolactinaemia respectively with a significant *p*-value = 0.014, while abdominopelvic mass was also found in 33.3% and 0.0% of subjects and controls with high serum prolactin values, with a significant *p*-value = 0.040. Other examination variables had no significant relationship between both groups.

Table 5: Comparison of Examination findings in subjects and controls with hyperprolactinemia

Examination findings	High Prolactin		OR (95% CI)	χ^2	*p*-value
	Subject n=30 (%)	Control n= 12(%)			
Facial hair					
Yes	5 (16.7)	3 (25.0)	0.600 (0.119 – 3.036)	0.386	0.534
No	25 (83.3)	9 (75.0)			
Acne					
Yes	4 (13.3)	0 (0.0)	NA	1.768	0.308
No	26 (86.7)	12 (100.0)			
Visual field					
Normal	21 (70.0)	11 (91.7)	0.202 (0.023 – 1.811)	2.372	0.124
Abnormal	9 (30.0)	1 (8.3)			
Galactorrhoea					
Yes	20 (66.7)	3 (25.0)	6.000 (1.324 – 27.191)	6.007	**0.014***
No	10 (33.3)	9 (75.0)			
Abdominal mass					
Yes	10 (33.3)	0 (0.0)	NA	5.250	**0.040***
No	20 (66.7)	12 (100.0)			

χ^2: Chi-square test; *: *p*-value < 0.05 (statistically significant); OR (95% CI): Odds ratio at 95% confidence interval

Table 6 shows the comparison of symptoms in subjects and controls with normal prolactin values. Cessation of menses and intermenstrual bleeding were not significantly different in the two groups with a *p*-value of 0.052 and 0.125 respectively.

Table 6: Comparison of Symptoms in subjects and controls with normal prolactin values

Symptoms	Normal Prolactin		OR (95% CI)	χ^2	*p*-value
	Subjects n = 23(%)	Control n =41 (%)			
Milky nipple discharge					
Yes	3 (13.0)	11 (26.8)	0.409 (0.101 – 1.653)	1.639	0.201
No	20 (87.0)	30 (73.2)			
Headache					
Yes	6 (26.1)	5 (12.2)	2.541 (0.679 – 9.508)	1.998	0.158
No	17 (73.9)	36 (87.8)			
Blurring of vision					
Yes	1 (4.3)	1 (2.4)	1.818 (0.108 – 30.510)	0.177	1.000

No	22 (95.7)	40 (97.6)			
Previous miscarriage					
Yes	7 (30.4)	11 (26.8)	1.193 (0.387 – 3.676)	0.095	0.758
No	16 (69.6)	30 (73.2)			
Cold intolerance					
Yes	1 (4.3)	2 (4.9)	0.886 (0.076 – 10.340)	0.009	1.000
No	22 (95.7)	39 (95.1)			
Weight gain					
Yes	4 (17.4)	6 (14.6)	1.228 (0.308 – 4.896)	0.085	1.000
No	19 (82.6)	35 (85.4)			
Decreased libido					
Yes	3 (13.0)	6 (14.6)	0.875 (0.197 – 3.886)	0.031	1.000
No	20 (87.0)	35 (85.4)			
Cessation of menses					
Yes	4 (17.4)	1 (2.4)	8.421 (0.880 – 80.565)	4.574	0.052
No	19 (82.6)	40 (97.6)			
Intermenstrual bleeding					
Yes	2 (8.7)	0 (0.0)	2.952 (2.085 – 4.180)	3.680	0.125
No	21 (91.3)	41 (100.0)			

χ^2: Chi-square test; *: *p*-value < 0.05 (statistically significant); OR (95% CI): Odds ratio at 95% confidence interval

Table 7: shows the comparison of examination findings in subjects and controls with normal prolactin values. Abdominal mass was found in 13.0% and 2.4% of infertile subjects and fertile controls with normal serum prolactin values, difference was not significant. Galactorrhoea was demonstrated in the same number of persons in both groups accounting for 47.8% and 26.8% in infertile subjects and fertile controls with no statistically significant difference between both groups.

Table 7: Comparison of Examination findings in subjects and controls with normal prolactin values

Examination findings	Normal Prolactin		OR (95% CI)	χ^2	*p*-value
	Subject n=23 (%)	Control n= 41(%)			
Facial hair					
Yes	1 (4.3)	3 (7.3)	0.576 (0.056 – 5.878)	0.222	1.000
No	22 (95.7)	38 (92.7)			
Acne					
Yes	0 (0.0)	7 (17.1)	NA	4.409	**0.043***
No	23 (100.0)	34 (82.9)			
Visual field					
Normal	18 (78.3)	35 (85.4)	0.635 (0.170 – 2.371)	0.460	0.511
Abnormal	5 (21.7)	6 (14.6)			
Galactorrhoea					
Yes	11 (47.8)	11 (26.8)	2.500 (0.857 – 7.294)	2.880	0.090
No	12 (52.2)	30 (73.2)			
Abdominal mass					
Yes	3 (13.0)	1 (2.4)	6.000 (0.586 – 61.419)	2.828	0.128
No	20 (87.0)	40 (97.6)			

χ^2: Chi-square test; *: *p*-value < 0.05 (statistically significant); OR (95% CI): Odds ratio at 95% confidence interval

Discussion

Hyperprolactinemia is a common problem encountered in reproductive disorders and it is described as the most effectively treatable cause of endocrine infertility (26). The mean age for the infertile subjects was 33.11 ± 5.62 years while that of fertile controls was 32.92 ± 4.82 years. Hyperprolactinaemia was recorded in about three-

fifths and one-fifth of infertile women and fertile controls respectively. The Mean serum prolactin value was higher among the infertile subjects than the fertile control and this was statistically significant (24.93 ± 16.51ng/ml vs 17.15 ± 8.05ng/ml, p = 0.003). Median serum prolactin values of infertile subjects with milky nipple discharge, decreased libido and galactorrhoea were significantly higher than those of fertile controls (p-value = 0.001, 0.033 and 0.016 respectively). Comparison of amenorrhoea, galactorrhoea and abdominopelvic mass were significantly related to hyperprolactinaemia in infertile subjects than in fertile controls (p-value = 0.040, 0.014 and 0.040 respectively).

In our study the range and mean of serum prolactin levels in the infertile women were 12-90ng/ml and 24.93±16.51ng/ml respectively while the prevalence of hyperprolactinemia was 56.6%. In a study done in Kano, the prevalence of hyperprolactinemia was 33.5%, with a higher mean serum value of 865 ± 68.9mIU/ml (40.8ng/ml) (27). The higher level of mean serum prolactin is likely because the subjects in their study were those with hyperprolactinemia when compared to ours in which the study population included both normoprolatinemia and hyperprolactinemia. Similarly in a study in Calabar, southern Nigeria, half of the subjects had elevated prolactin values and a much higher mean of 63.09 ± 61.78ng/ml was documented among the infertile women with hyperprolactinaemia (6). The higher mean recorded in the hyperprolactinemic infertile group in Calabar, despite having a similar definition of hyperprolactinaemia with this study (reference range used is 8.39-20.15ng/ml) might be due to the separation of the infertile group into those with hyperprolactinaemia and those with normal values. However, in Sudan, Northern Africa one-third of the infertile women were hyperprolactinemic with a mean serum prolactin level in the study group of 428.85 ± 361.82mIU/ml (20.2 ±17.1ng/ml) (23) which is similar to the value in this study, likewise in India, almost three-fifths of the infertile population had hyperprolactinaemia with a mean value of 21.52 ± 17.71ng/ml (15) which is also similar to the findings in the present study. Infertile women may, however, have normal serum prolactin values as seen in a little above two-fifths of the infertile subjects in this study, even in the presence of symptoms suggestive of hyperprolactinaemia (28). Infertility in such a group of persons may be due to other anovulatory causes of infertility.

The Mean of the serum prolactin levels in the fertile controls in the study was 17.15 ± 8.05ng/ml and a range of 7-55ng/ml. This mean is higher than that reported in a Calabar study (6) (8.21 ± 3.71ng/ml) and a central Sudan study (9.50 ± 4.31ng/ml) (26). However, an Indian study despite being a retrospective study recorded a similar mean value of 15.22±9.54ng/ml in the fertile controls, also 13 of the 50 (26%) controls had elevated serum prolactin values (15) as compared to 12 of 53 (22.6%) fertile controls in the present study. The difference in the mean values in the different studies might be related to the group of persons used as controls. The controls used in the Calabar study were described as healthy women with proven fertility who were ensured to be normoprolactinaemic while controls in this study were healthy female hospital staff who did not necessarily have normal levels but were recruited based on their fertility status.

Hyperprolactinaemia in fertile women as seen in just above one-fifth of fertile controls in this study may be explained by the variable molecular heterogeneity of the prolactin hormone (28). Also in less severe cases, high prolactin levels may only disrupt ovulation once in a while; this results in intermittent or occasional ovulation with oligomenorrhoea and this explains why some women adjudged fertile may have high serum prolactin levels.

Comparison between the mean serum prolactin value of the infertile subjects and that of the fertile controls was significant. This agrees with the findings in studies done in India, Sudan and Calabar (6, 15, 23).

A search of the literature shows different clinical features of hyperprolactinaemia such as shortened luteal phase, oligomenorrhoea, amenorrhoea, galactorrhoea, decreased libido and visual field defects (23, 26, 27, 29, 30). Studies have also quoted galactorrhoea as being the most common symptom of hyperprolactinaemia (31, 32), while other studies reported that two-thirds of patients with both galactorrhea and amenorrhea will have hyperprolactinemia (26, 28). In this study, the median serum prolactin value of infertile subjects with a history of milky breast discharge and demonstrable galactorrhoea was significantly higher than the median serum prolactin value of fertile controls with the same history and finding respectively. Similarly, the comparison of galactorrhoea in both infertile subjects and fertile controls with hyperprolactinaemia was significant; also, more than half of infertile subjects complained of milky nipple discharge while two-thirds of them had demonstrable galactorrhoea. A study done at Visakhapatnam, India found that the difference in the incidence of galactorrhoea in infertile women

with or without hyperprolactinaemia was significant, and a greater proportion of infertile women with hyperprolactinaemia had galactorrhoea when compared to those with normal serum prolactin values and vice versa (26). This finding is comparable to reports from a similar study in Port Harcourt, Nigeria (31). However, in Jigawa, North West Nigeria, even though higher mean prolactin values were recorded among infertile patients with galactorrhoea, only 36.7% had elevated serum prolactin levels (32). Among a much older age group in a study recently conducted at the ART unit, UITH, just above two-fifths of the hyperprolactinemic group had galactorrhoea (33). Galactorrhoea is a sign of hyperprolactinaemia but prolactin may be normal in patients with milky nipple discharge (31).

Lower scores for sexual function and desire have also been found in women with hyperprolactinaemia who have regular menses (34). This study found a significant difference in the median serum prolactin levels of infertile subjects and fertile controls.

In Visakhapatnam, India about four-fifths of infertile women with hyperprolactinaemia compared with a little below one-third of normoprolactinaemic infertile women, presented with menstrual irregularities (26) and in Sudan mean prolactin level was elevated in infertile women with menstrual irregularities (23). In this study, one-third of infertile subjects with hyperprolactinaemia had a history of cessation of menses and this was significantly higher than fertile controls with similar elevated serum prolactin values. Similar to findings in Sudan (23), a higher median serum prolactin value was recorded in subjects with a history of cessation of menses than in controls though without statistical significance. A previous study has reported that many women also do not have menstrual irregularities/abnormalities despite elevated serum prolactin levels (16).

Clinical findings such as milky nipple discharge, galactorrhoea, decreased libido, abnormality in menstrual pattern, and abdominopelvic masses may predict hyperprolactinaemia in infertile patients, serum prolactin levels may be normal in some women with these features. The decision to treat hyperprolactinaemia in the presence or absence of these symptoms will depend on the serum prolactin value, severity of symptoms and desire for fertility.

Study strengths and limitations

Examinations and assessments in this study were done by one person, hence removing inter-observer error and improving the reliability of findings. Prolactin level of fertile controls is suggestive of possible local reference value expected in the study population. This may form a template for future studies.

This study was limited by its design as a hospital-based study without provision for other affected women in the community. A community-based study could have removed this limitation. In addition, the time frame for the study was limited; therefore, follow-up of participants for treatment modalities and outcomes were not included in the study. The non-probability sampling may limit the generalization of findings for normal values. Regression analysis was not used.

Conclusion

Serum prolactin levels of infertile women attending the gynaecologic clinic in UITH were significantly higher than fertile controls. Prevalence of hyperprolactinaemia was higher among the infertile subjects and clinical features were more demonstrable in fertile controls than infertile subjects.

Empirical treatments of infertile women with milky nipple discharge and galactorrhea should be considered while awaiting biochemical results of prolactin assay. In infertile women, clinical findings of hyperprolactinaemia will further support the need for treatment. The reference range of serum prolactin values in asymptomatic fertile women can be used as a baseline in future studies to develop a nomogram.

List of Abbreviations

ART: Assisted Reproductive Technology
LH: Luteinizing Hormones
mIU: Micro International Unit
ml: Millilitre
ng: Nanogram
PID: Pelvic Inflammatory Disease
SPSS: Statistical Packet for Social Sciences
STDs: Sexually Transmitted Diseases
UITH: University Of Ilorin Teaching Hospital
WHO: World Health Organization

Declarations

Ethical approval and consent to participate

Institutional approval for this study was obtained from the Ethical Review Committee of the University of Ilorin Teaching Hospital (ERC PAN/2016/04/0527) before the commencement of the study. Informed written consent was obtained from each participant after adequate counseling and the data obtained from the study was treated with confidentiality and used solely for the study.

Consent for publication
All authors gave consent for publication of the work under the Creative Commons Attribution-Non-Commercial 4.0 license.

Availability of data and materials
All essential data supporting the findings of this case are available within the article. Additional data are available upon request from the corresponding author.

Competing interests
There was no conflict of interest in the conduct of this study.

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Authors' contributions
DJK: Concept, Data collection and / or processing, writer, Funding; BTY: Literature review, Analysis and / or interpretation, Funding; EGG: Design, Materials, Funding; AMG: Literature review, Funding; SHA: Data collection, Funding; AKT: Supervision, Funding, Critical review; JAAG: Supervision, Funding, Critical review; BSA: supervision, funding and analysis.

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