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Serum fertility profile in infertile women in Calabar

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Abstract

This study was aimed to determine follicle stimulating hormone (FSH), luteinizing hormone (LH), Prolactin (PRL), progesterone (PROG), and estradiol (E2) levels in infertile women in Calabar. A total of ninety (90) subjects which comprises of thirty (30) menorrheic infertile women, thirty (30) amenorrheic infertile women and thirty (30) controls were enrolled into the study. The infertile women were further grouped into twenty three (23) primary and thirty seven (37) secondary infertile women. Blood samples were collected from menorrheic infertile women and control on third and twenty first day of the menstrual cycle. FSH, LH, estradiol, and prolactin were analysed using day three serum samples, while progesterone was analyzed using day twenty first samples using ELISA method. Random blood samples were collected from amenorrrheic infertile women and were assayed for FSH, LH, E2, prolactin, progesterone using ELISA method. Anthropometric indices and sociodemographic information were obtained using standard methods. Data were analyzed using student t-test, one-way analysis of variance (ANOVA). Significant difference was considered at $p < 0.05$. The mean levels of FSH, LH, and prolactin were significantly higher ($p = 0.001$) while progesterone was significantly lower ($p=0.001$) in infertile women when compared to control. The WHR was significantly higher ($p=0.037$) in the secondary infertile women compared to the primary infertile women. Lower level of progesterone and higher levels of FSH, LH and prolactin may be associated with female infertility in Calabar. It is recommended that early estimation of these hormonal parameters and their management would possibly lead to increased chances of conception.

Keywords: Infertility; Follicle stimulating hormone; Luteinizing hormone; Estradiol; Progesterone; Prolactin

1. Introduction

Infertility is defined as the inability to conceive after one year or more of regular unprotected sexual intercourse [1]. It could be primary in nature, i.e when both partners have never conceived in their lifetime or secondary, i.e, inability of couples or partners to conceive after a year when one or both partners have previously had a child or children [2]. According to the World Health Organisation, about 10% - 25% of the couples complain of infertility disorder. It affects approximately 60 – 80 million couples world wide [5]. Prevalence of infertility is higher in sub –Saharan Africa, with 10% - 30% of couples affected in Nigeria [7].

There are so many factors that contribute to infertility. The factors can be grouped into male factors, female factors, combine male and female factors and idiopathic factor, where no obvious cause could be detected. The most common causes in relation to the male factor include sperm abnormalities [8]. The female factors on the other hand include blockage of the fallopian tube due to malformations, infections such as Chlamydia trachomatis or scar tissue, endometriosis due to the growth of endometrial tissue in the fallopian tube or around the ovaries, and ovulatory disorders such as oligo-ovulation or anovulation [20]. Other factors include malformation of the egg due to polycystic

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ovarian syndrome (PCOS), being overweight or underweight or age as female fertility declines after the age of thirty [35].

Hormonal disturbances have been considered of great importance in the cause and diagnosis of female infertility. Follicle stimulating hormone (FSH) stimulates the growth of the follicles; luteinizing hormone (LH) stimulates ovulation; both of which are produced in the anterior pituitary gland. Estradiol, on the other hand is produced in the ovaries. It stimulates the growth of the endometrium during menstrual cycle. An elevated estradiol level mid-cycle causes an increase in LH, which triggers ovulation [6]. An increase in FSH in women may indicate a reduction in the production of good quality eggs and embryos for fertilization [14]. Higher than normal levels of LH in a woman may mean the ovaries are absent or not functioning. Low levels of LH may indicate anorexia, an issue in the pituitary gland, stress, or damage to the hypothalamus in both men and women [15]. Prolactin, also produced in the anterior pituitary gland, interacts with the breasts and ovaries. It stimulates the growth of the mammary glands during pregnancy, as well as milk production after birth. High level of prolactin (hyperprolactinaemia) may inhibit ovulation. Progesterone together with oestradiol helps to prepare the endometrium to receive the fertilized egg. During pregnancy, progesterone also supports the endometrium so that it does not shed [6].

1.1. Statement of the Problem

Infertility is a growing gynaecological problem in our environment with a rising number of women within reproductive age having difficulty becoming pregnant [13].There is a wide variation in the incidence of infertility, in different parts of the world, being highest in the so-called infertility belt of Africa, which includes Nigeria [11]. It has been attributed to high rate of sexually transmitted diseases, complications of unsafe abortion and puerperal pelvic infections [16]. Hospital-based prevalence of infertility reported in some parts of Nigeria are 15.7% from Sokoto (North West) [18], 23.9% from Bauchi (North East) [9], 4.0% from Ilorin (North Central), [3], 15.4% in Abakaliki (South East) [17], 48.1% in Osogbo (South west) [4] and 34 per 1000 in Calabar (South South) [10]. Infertility affects millions of people and has an impact on their families and communities. Estimates suggest that approximately one in every six people of reproductive age worldwide experience infertility in their time [21]. Fertility hormones are routinely measured to assess ovarian cause of female infertility. However, females with normal hormonal levels may have difficulty in conception and vice versa. This study is to determine the hormonal cause of female infertility in our locality.

Aim of the Study

The aim of the study is to evaluate serum follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), progesterone (PROG), and estradiol (E2) levels in infertile women.

Objectives of the Study

- To determine and compare the follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), progesterone (PROG), and estradiol (E2) in infertile women and control.
- To compare the levels of these parameters between menorrheic and amenorrheic infertile women and control.
- To compare the levels of the hormones based on the types of infertility and BMI.

1.2. Research question

Is there any significant difference in the serum concentration of fertility hormones in infertile women and control?

1.3. Research hypothesis

There is no significant difference between serum concentration of fertility hormones in infertile women and control.

2. Materials and methods

2.1. Study Area

The subjects of the study were recruited from the Gyneacology Clinic of the University of Calabar Teaching Hospital. Calabar is the capital city of Cross River State, Nigeria. It was originally named Akwa Akpa, in the Efik language. The city is adjacent to the Calabar and Great Kwa rivers and creeks of the Cross River (from its inland delta).

Calabar is often described as the tourism capital of Nigeria. Administratively, the city is divided into Calabar Municipal and Calabar South Local Government Areas. It has an area of 406 square kilometres (157 sq mi) and a population of 371,022 as at 2006 census [19].

2.2. Study Design

The study design was a comparative cross sectional study.

2.3. Study Population

A total of ninety (90) participants were recruited for the study. Thirty (30) were menorrheic infertile women, thirty (30) were amenorrheic infertile women attending Gyneacology Clinic of the University of Calabar Teaching Hospital and thirty (30) were enrolled as control (i.e. women who have given birth in the last two years). The infertile women were further grouped into twenty three (23) primary and thirty seven (37) secondary infertile women. The diagnosis and selection was done with the help of a Gynaecologist in the Obstetrics and Gynaecology Department of the Hospital.

2.4. Data Collection

Socio demographic data were collected using questionnaire. Detailed information about the study was explained to the participants and consent was obtained before patients sample and data were collected.

2.5. Sample Size Determination

The sample size was calculated from the formula [33].

$$N = Z^2pq/d^2$$

Where N = minimum sample size
Z = area under normal curve corresponding to 95% confidence interval
p = 6% [34].
q = 1- p = 0.87
d = the level of statistical significance = 0.05

N = 80

An attrition of 10% was added, a total of 90 was used.

2.6. Sample Collection, Processing and Storage

A standard venepuncture method was used to obtained five millilitres (5ml) of whole blood each from menorrheic infertile women and control on day three (3) and day twenty one (21) of the menstrual cycle and five millilitres (5ml) of random blood samples from amenorrheic infertile women into plain tubes. They were labelled appropriately and allowed to clot at room temperature. The sera were separated from the red cell by spinning at 3,000 rpm for 5 minutes. The supernatant obtained was stored frozen at -20^{0}C until the day of analysis. FSH, LH, estradiol, and prolactin were analysed on day three serum samples, while progesterone on day twenty one serum sample. FSH, LH, estradiol, prolactin, and progesterone were analysed on random serum samples using enzyme link immunosorbent method.

2.7. Anthropometric Parameters

The Height (Metres) and weight (Kg) of participants were measured using a stadiometer and digital weighing scale. Body mass index (BMI) was calculated using the formula: weight/height^2 in the morning on same day of biochemical sample collection. The waist circumference in centimetre was measured in the distance around the smallest part of the waist, just above the belly button. The hip circumference in centimetre was determined by measuring the distance around largest part of the hips. Waist-to-Hip (W/H) ratio was obtained by dividing the waist circumference by the hip circumference [22].

3. Results

Table 1 shows the socio-demographic characteristics of the study population, consisting of ninety (90) subjects, distributed as follows: thirty (30) in the control group, thirty (30) in the amenorrheic infertile group and thirty (30) menorrheic infertile group. Out of the total subjects, 26(28.9%) had normal body mass index (BMI) (18-24 kg/m^2), 36(40.0%) were overweight (25-29 kg/m^2) and 28(31.1%) were obese (>30kg/m^2). The overweight BMI classification was the most common across all groups, with 40% of the total population falling into this category. The number of infertile patients that presented with primary infertility was 23 (38.3%) and secondary infertility was 37 (61.7%).

Secondary infertility was more prevalent in the amenorrheic infertile group, 20 (33.3%) accounting for the total infertile cases.

Table 1 Socio-demographic characteristics of the study population

Parameter	**Menorrhea n = 30 n (%)**	**Amenorrhea n = 30 n (%)**	**Control n = 30 n (%)**	**Total**	**Statistics**
BMI Classification					
Normal	9(10.0)	8(8.9)	9(10.0)	26(28.9)	$\chi2 = 0.148$ $p = 0.997$
Overweight	12(13.3)	12(13.3)	12(13.3)	36(40.0)	
Obesity	9(9.0)	10(11.1)	9(9.0)	28(31.1)	
Type of infertility					
Primary	13(21.7)	10(16.7)	-	23(38.3)	$\chi2 = 0.635$ $p = 0.425$
Secondary	17(28.3)	20(33.3)	-	37(61.7)	
Marriage duration					
≤ 5 years	29(32.2)	12(13.3)	23(25.6)	64(71.1)	$\chi2 = 24.123$ $p = 0.001$*
> 5 years	1(1.1)	18(20.0)	7(7.8)	26(28.9)	
Educational Status					
Primary	11(12.2)	0(0.0)	0(0.0)	11(12.2)	$\chi2 = 30.115$ $p = 0.001$*
Secondary	11(12.2)	23(25.6)	18(20.0)	52(57.8)	
Tertiary	7(7.8)	7(7.8)	12(13.3)	26(28.9)	
None	1(1.1)	0(0.0)	0(0.0)	1(1.1)	
Employment status					
Civil servant	7(7.8)	9(10.0)	12(13.3)	28(31.1)	$\chi2 = 3.228$ $p = 0.520$
Trading Unemployed	10(11.1) 13(14.4)	10(11.1) 11(12.2)	11(12.2) 7(7.8)	31(34.4) 31(34.4)	

*= Significant at $p < 0.05$

Table 2 Comparison of mean age, BMI, WHR, and the female hormones in infertile women and control

Parameter	**Infertile Women n = 60**	**Control n = 30**	**t-value**	**p – value**
AGE (years)	32.13±4.97	30.57±4.46	1.458	0.148
BMI (kg/m^2)	26.56±6.13	26.27±6.17	0.212	0.833
WHR	0.79±0.07	0.77±0.06	1.189	0.237
FSH (miu/ml)	21.24±5.12	7.54±1.56	4.030	0.001*
LH (miu/ml)	20.56±4.54	5.70±1.17	5.556	0.001*
Prolactin (miu/ml)	40.26±5.77	8.18±3.53	7.368	0.001*
Estradiol(pg/ml)	107.40±37.92	82.22±20.77	1.383	0.171
Progesterone (ng/ml)	6.58±7.83	19.31±2.58	-11.417	0.001*

Values are expressed as mean ± SD. Where BMI = Body mass index, WHR = Waist hip-ratio, FSH = Follicle stimulating hormone, LH = Luteinizing hormone; * significant at $p < 0.05$

Out of the total participants, 26 (28.9%) had been married for more than 5 years with amenorrheic infertile women accounting for 18 (20.0%), and 64 (71.1%) had been married for less than or equal to 5 years with menorrheic infertile women accounting for 29(32.2%). Secondary educational status was the most common in all groups, with the highest frequency in the amenorrheic infertile women, comprising of 23 (25.6%). Additionally, the study found statistically significant differences (p = 0.001) in the marriage duration and educational status categories.

Table 2 shows the comparison of the mean values of age, body mass index, waist-hip ratio, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol, and progesterone between the infertile women and control. The mean levels of FSH, LH, and prolactin were significantly higher (p = 0.001) while progesterone was significantly lower (p = 0.001) in infertile women when compared to control. However, the mean age, BMI, WHR, and estradiol in infertile women were not significantly different (P>0.05) from the values in control subjects.

Table 3 Comparison of mean age, BMI, WHR, and the female hormones in menorrheic infertile women, amenorrheic infectile women and control

Parameter n = 30	**Menorrheic Infertile women**	**Amenorrheic infertile women n = 30**	**Control n = 30**	**F-ratio**	**p – value**
AGE (years)	32.0±5.21	32.13±4.97	30.57±4.46	1.074	0.346
BMI (kg/m2)	26.36±6.04	26.75±6.32	26.27±6.17	0.052	0.949
WHR	0.79±0.05	0.79±0.09	0.77±0.06	0.748	0.476
FSH(miu/ml)	14.67±3.86	27.80±5.74	7.54±1.56	7.247	0.001*
LH (miu/ml)	9.53±2.73	31.59±4.87	5.70±1.17	28.476	0.001*
Prolactin (miu/ml)	44.22±5.57	36.30±5.97	8.18±3.53	14.393	0.001*
Estradiol(pg/ml)	107.17±12.68	107.63±10.64	82.22±4.56	0.486	0.617
Progesterone (ng/ml)	9.86±2.98	3.29±2.21	9.31±2.58	53.537	0.001*

Values are expressed as mean ± SD. Where BMI = Body mass index, WHR = Waist hip-ratio, FSH = Follicle stimulating hormone, LH = Luteinizing hormone; * significant at p < 0.05

Table 3 shows the comparison of the mean values of age, body mass index, waist-hip ratio, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol, and progesterone among the menorrheic infertile women, amenorrheic infertile women and control. Significant variations (P < 0.05) were observed among the groups in FSH, LH, prolactin, and progesterone.

Table 4 Comparison of mean age, BMI, WHR, and the female hormones in infertile Women based on the type of infertility

Parameter	**Primary 23**	**Secondary 37**	**t-value**	**p – value**
AGE (years)	32.00±5.17	32.22±4.91	-0.163	0.871
BMI (kg/m2)	25.91±6.62	26.96±5.86	-0.647	0.520
WHR	0.77±0.06	0.81±0.07	-2.137	0.037*
FSH (miu/ml)	24.11±5.60	19.45±4.77	0.667	0.508
LH (miu/ml)	24.05±5.21	18.39±3.92	0.914	0.368
Prolactin (miu/ml)	35.12±4.55	43.46±6.26	-0.940	0.351
Estradiol(pg/ml)	108.60±10.77	106.60±12.31	0.053	0.958
Progesterone (ng/ml)	7.74±3.05	5.85±2.60	0.907	0.368

Values are expressed as mean ± SD. Where BMI = Body mass index, WHR = Waist hip-ratio, FSH = Follicle stimulating hormone, LH = Luteinizing hormone; * significant at p < 0.05

Table 4 shows the comparison of the mean values of age, body mass index, waist-hip ratio (WHR), follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol, and progesterone in infertile women based on the type of infertility. The WHR was significantly higher ($p = 0.037$) in the secondary infertile women compared to the primary infertile women. There were no significant differences ($p > 0.05$) in the mean levels of FSH, LH, estradiol, progesterone and prolactin in women with primary infertility when compared with secondary infertility.

Table 5 Comparison of mean age, BMI, WHR, and the female hormones in infertile women based on body mass index classification

Parameter	Normal n = 17	Overweight n = 30	Obesity n = 30	F- ratio	P – value
AGE (years)	31.47±4.80	33.13±4.80	31.47±5.36	0.796	0.458
WHR	0.77±0.09	0.79±0.06	0.82±0.05	2.467	0.094
FSH(miu/ml)	15.03±3.16	24.51±5.39	22.65±5.67	0.683	0.509
LH(miu/ml)	23.76±4.88	18.83±4.37	22.65±5.67	0.291	0.749
Prolactin (miu/ml)	36.05±6.25	37.52±4.79	47.48±6.26	0.655	0.523
Estradiol(pg/ml)	150.62±13.77	93.62±10.31	89.14±10.77	1.187	0.312
Progesterone(ng/ml)	6.32±2.67	6.84±2.94	6.47±2.79	0.024	0.976

Values are expressed as mean ± SD. Where BMI = Body mass index, WHR = Waist hip-ratio, FSH = Follicle stimulating hormone, LH = Luteinizing hormone; * significant at $p < 0.05$

Table 5 shows the comparison of the mean values of age, body mass index, waist-hip ratio, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol, and progesterone in infertile women based on BMI. There were no significant variations ($P > 0.05$) observed in these parameters.

4. Discussion

Infertility is a serious reproductive health concern amongst many women in Nigeria with associated psychosocial impact. There is a need for early diagnosis of this disorder for increased chances of fertility in Nigerian women. This study showed that the age of infertile women was higher than control but was not statistically significant. [23] demonstrated the decline in female fertility starting at 31 years of age. The means BMI and WHR were higher in the secondary infertile women than the primary infertile women. However, the mean BMI was not statistically significant while the mean WHR was statistically significant between the two groups. This could be due to fat accumulation either due to previous pregnancy, nutritional modifications, or it could be a phenomenon linked to age [29]. Secondary infertility was found in the majority of the participants in the study group compared with primary infertility. This is similar with findings from several other studies in sub-Saharan Africa [18]. However, primary infertility has been found to be commoner in western countries [31]. The high prevalence of secondary infertility in developing countries has been attributed to high prevalence of sexually transmitted infections and inadequate treatment of such infections, complications of unsafe abortion and puerperal sepsis [31].

The mean value of LH among the infertile women in this study was higher when compared with the mean value of LH in the fertile group and was statistically significant. This agrees with the results reported by [25] and contradicts the result reported by [27], who found no significant difference in serum LH between infertile group and control group. The difference could be due to early reduction in ovarian reserve in the infertile group. Elevated serum LH level in infertile women could lead to a significant reduction in the rate of fertilization, increased risk of spontaneous miscarriages, and there could be failure of conception [32]. The mean value of FSH among the study participants was also found to be higher as compared with the control and this was statistically significant. This was comparable to the results by [30] and disagrees with result reported by [26], who did not find any significant difference in basal serum FSH between the infertile group and the control group. Elevated FSH levels represented a declining ovarian reserve and an increased day 3 FSH level is considered as a late indicator of the marked decreased fertility potential. The mean value of prolactin (PRL) was significantly higher in infertile group than in the control group. This agrees with result reported by [30]. This may be attributed to several effects that interfere with ovulation leading to infertility; this includes decrease of Gonadotrophin Releasing Hormone (GnRH), inhibition of LH and FSH release and inhibition of both Oestrogen and Progesterone secretion in the ovary [28]. Infertile women had significantly lower progesterone than fertile women but there was no significant difference in their estradiol level. This is in agreement with the previous studies of [24], who reported similar pattern of results which may have accounted for primary hypogonadism in these infertile subjects.

This is in consistent with the works of [26], who found a significantly lower progesterone level between infertile and fertile women. It disagrees with results reported by [26], who found a significantly lower estradiol and a significantly higher estradiol level by [27], between infertile group and control group.

5. Conclusion

This study has shown that infertile women have significantly lower level of progesterone and significantly higher levels of follicle stimulating hormone, luteinizing hormone and prolactin, suggesting their roles in female infertility.

Recommendation

A large number of prospective studies are still needed to assess the causal relationship between these hormones and other factors that contribute to infertility. It is recommended that early estimation of these hormonal parameters and their management would possibly lead to increased chances of conception in infertile women.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have declared that no conflicts of interests exist.

Statement of ethical approval

Ethical approval for the study was obtained from Cross River State Health Research Ethics Committee, Ministry of Health.

Statement of informed consent

Informed consent was obtained from all participants before they were enrolled for the study.

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