International Journal of Research in Medical Sciences
Abriba SP et al. Int J Res Med Sci. 2020 Apr;8(4):1514-1522
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20201352

Original Research Article

Evaluation of hormonal profile and some stress biomarkers in infertile couples in Abuja, Nigeria

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Received: 08 February 2020
Revised: 25 February 2020
Accepted: 29 February 2020

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ABSTRACT

Background: Infertility is a growing gynaecological problem in couples of childbearing age having difficulties bearing children. Couples with infertility are known to present with high levels of stress and psychopathology A cross sectional case control study aimed at evaluating the hormonal profile, some stress biomarkers, sperm analysis in infertile couples was carried out to ascertain their contributions to infertility in couples of child bearing age.
Methods: Serum Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Prolactin, Progesterone, Estrogen (E2), Testosterone, Salivary Cortisol and Salivary Alpha Amylase were evaluated using both competitive and non-competitive Enzyme Linked Immunosorbent Assay (ELISA) techniques; while sperm cells analysis were evaluated using conventional methods, in 164 infertile couples (study) and 100 fertile couples (control) attending fertility clinic in General Hospitals in Abuja, Nigeria.
Results: The mean serum Prolactin and Salivary (S) Cortisol in the female were significantly higher ($p<0.05$) in the study group relative to the control group, while Salivary Alpha Amylase and LH show no significant difference ($p>0.05$) between the two groups. FSH, Progesterone and E2 in the female were significantly lower in the study group ($p<0.05$) compared with control group. Testosterone, FSH, Sperm cells count and Sperm activity (%) were significantly lower ($p<0.05$) in the male study group relative to the control group; while prolactin, S. cortisol and S. amylase were significantly higher ($p<0.05$) in the male study group relative to the control group.
Conclusions: Abnormal hormones values and abnormal sperm quality and quantity are associated with elevated stress biomarkers in couples presenting with infertility. Strong positive correlations exist between hormones and stress biomarker in infertility conditions.

Keywords: Biomarkers of stress, Couples infertility, Hormonal profile, Sperm cells count

INTRODUCTION

Infertility is a growing gynecological public health problem in our communities with couples of childbearing ages having difficulty becoming pregnant.[1] The failure to achieve the clinical pregnancy after 12 months or more of regular unprotected sexual intercourse is referred to as infertility.[2] Infertility could either be primary or secondary: Primary, when the partners have never conceived in their lifetime and Secondary, when the couples could not get a child after they have had some children or a child.[3]

Primary infertility in couple who have never had a child may include being unable to conceive, being unable to maintain pregnancy to full term or being unable to carry a pregnancy to a live birth.[4] Infertility is generally said to occur in 8- 12% of couple globally.[3]

In many cultures around the world, infertility has a very strong social stigma, especially in its relations to women, depending on their cultural context. Reproduction, in basic human instincts, represents a continuation of the family and the survival of species. Therefore, fertility is respected and almost revered in most culture around the world.[5]

Couples currently experiencing infertility problems display more depression and anxiety than counterparts who have eventually conceived naturally.[6]

Although most researchers have rejected the notion that psychopathology is an important causal factor in infertility, there is a support for the cyclical argument that infertility produces stress, and that stress in turn inhibits fertility.[7-10]

Infertility is the major reason for gynecological visit to the healthcare provider and couples visiting to seek help can place heavy burden on limited health facilities.[11]

Due to the great importance attached to fertility in most cultures; therefore, infertility will have a greater impact on relationships in the developing world. Evidence for this claim comes from research showing that infertility is more strongly associated with psychopathology in Nigeria, a polygamous society.[12]

A lot of issues have been believed to cause infertility in couples of child bearing age, these could be hormonal imbalance, genital or urinary tract infections, abnormal sperm count in the male and stress which actually play a role in up to 30% of all problems of infertility.[13]

In the evaluation of infertile couples, stress biomarkers, semen analysis and hormonal profile was carried out to ascertain their contributions to infertility in couples of reproductive ages.

METHODS

This study is a cross sectional study carried out between January 2017 to December 2018 to determine the various hormones, some stress biomarkers and semen analysis in couples with infertility attending General Hospitals in Abuja, Nigeria and to correlate them with infertility conditions. All couples within the reproductive age (18-45 yrs) without any use of contraceptive were included; while those using contraceptive, below 18 yrs and above 45 yrs were excluded; 264 subjects were involved in the study, which consist of 164 infertile couples (study) and 100 fertile couples (control). Five milliliters of blood sample was drawn from each of the subject from the articular vein on their clinic visit days and day 21 of the female study subjects who had normal regular menstrual period for Progesterone estimation; the sample were allowed to clot after which, it was spin at 3000rpm for 5 minutes; serum sample was then extracted from the clotted sample and then refrigerated at the temperature of 4-8 degree centigrade until analysis. The Saliva sample was collected into a universal container containing a preservative, Sodium benzoate, the Saliva sample was stable until analysis. The male participants were instructed to collect the semen sample after abstinence for 3-5 days, through withdrawal or masturbation into clean universal container, the semen samples were analyzed within 30-60 minutes after collection using conventional methods. The hormones and biomarkers were measured by Enzyme Linked Immunosorbent Assay (ELISA) technique based on the competitive and noncompetitive sandwich principle, in accordance with the methods provided by diagnostic reagent kit supplied by Darlez Nig Ltd. The Statistical Package for Social Science (SPSS) window version 20.0 was used for all calculation and data analysis, p value <0.05 were considered statistically significant.

RESULTS

This study examined the hormonal profile and some stress biomarkers in infertile couples and the semen analysis of the male participants in Abuja, Nigeria. The subjects consist of 164 who are known with infertility condition as study group and 100 subjects without the condition of infertility as control group. The demographic and gynecological characteristics of the infertile and fertile couples are presented in Table 1. The mean Hormones and Biomarkers in the study group and control group in female category are presented in Table 2. The comparisons of measured Hormones and Biomarkers according to gonadotropic state in the female category are presented in Table 3. The comparisons of measured Hormones and Biomarkers according to prolactin state in female category are presented in Table 4. The mean Hormones, Biomarkers and Sperm parameters in the male study and control groups are presented in Table 5. The comparison of measured Hormones and Biomarkers according to semen quality of male category are presented in table 6. The correlation of biomarkers with various fertility conditions are presented in tables 7-9.

Table 1: Demographic and gynecological characteristics (mean±sd) of infertile and fertile participants.

Characteristics	Study group (164)	Control group (100)	p-values
Age (f)	32.0 ±4.2	30.35±4.2	>0.05
(m)	33.07±4.56	32.25±4.14	>0.05
Age at menarche	14.5±2.4	14.4±2.6	>0.05
Duration of menstrual cycle (days)	59.5±3.1	28.0±2.5	<0.05
Duration of menstrual flow (days)	4.0±0.5	4.7±0.6	> 0.05

Duration of infertility in the study group = 4 years. F = Female; M = Male

The mean and standard deviation of the demographic and gynecological characteristics of the infertile and fertile

couples in the study are presented in Table 1. The infertile women in the study group had a mean age 32.0±4.3 years, while the fertile women in the control group had a mean age 30.35±4.2 years. The mean age, age at menarche and duration of menstrual flow of the infertile women were not statistically different from those of the fertile women (p>0.05). However, the duration of menstrual cycles was significantly higher (p<0.05) in infertile women than the fertile women (59.5±3.1 days versus 28.0±2.5 days).

Table 2: Mean SD, hormones and biomarkers in the study and the control groups in the female category.

Parameter	Study group Mean±sd	Control group Mean±sd	Normal value	p-value
FSH (miu/ml)	5.92±1.77	12.03±14.71	2.0-12.0	<0.001
LH (miu/ml)	9.79±13.32	8.88±1.96	0.5-10.5	>0.001
Prolactin(ng/ml)	23.93±25.92	8.56±3.34	1.2-19.5	<0.001
Progesterone (ng/ml)	6.49±5.16	8.51±3.55	2.5-25.0	0.009
Day 21(ng/ml)	4.9±7.12.23	8.51±3.55	2.5-25.0	<0.001
Estrogen (pg/ml)	58.53±19.36	73.86±21.33	55.0-175.0	<0.001
S. Cortisol (microm/l)	373.17±47.79	306.63±67.36	221.0-550.0	<0.001
S. Amylase (u/l)	11.61±9.11	9.02±1.81	<15.0	0.001

Keys: LH = Luteinizing Hormone; FSH = Follicle Stimulating Hormone; S = Salivary

The mean FSH concentration of the Study Group (5.92±1.77 miu/ml) were statistically significant (p<0.05) when compared with the Control Group (12.03±14.71 miu/ml); mean LH of the Study Group (9.79±13.32 miu/ml l) show no significant difference (p>0.05) when compared with the Control Group (8.88±1.96 miu/ml); mean value of the Prolactin of the Study Group (23.93±25.92 ng/ml) was statistically higher (p<0.05) than the Control Group (8.56±3.34 ng/ml). The progesterone in the Study Group (6.49±5.16 ng/ml) was significantly lower (p<0.05) than the Control Group (8.51±3.55 ng/ml); the 21-day progesterone of some female study subjects was significantly lower than the control group. The estrogen was significantly lower (p<0.05) in the Study Group (58.53±19.36 pg/ml) than the Control Group (73.86±21.33 pg/ml). Salivary Cortisol was significantly higher (p<0.05) in the Study Group (373.17±147.79 micromol/L) than Control Group (306.63±67.36 micromol/L), the Salivary Alpha Amylase was significantly higher (p<0.05) in the Study Group (11.61±9.11U/L) than the Control Group (8.02±1.81U/L) as shown in Table 2.

Table 3: Comparison of hormones and biomarkers according to gonadotropic state in the female category.

Variables	Control group (50)	Study group (82)		p-value	sig
		Normogonadotropic Mean± sem N=64 (78.0%)	Hypergonadotropic Mean± sem N=18(22.0%s)		
LH (miu/ml)	8.88±1.96	7.39±3.30	23.63±24.04	0.0001	S
FSH (miu/ml)	12.03±14.71	7.39±4.01	28.20±24.55	0.0001	S
Prolactin (ng/ml)	8.59±3.36	26.04±28.39	15.50±10.02	0.0001	S
Progesterone (ng/ml)	8.48±3.59	6.75±5.58	5.73±3.12	0.048	S
Estrogen (pg/ml)	73.84±21.46	59.77±20.59	54.22±12.89	0.0001	S
S. Cortisol (microm/l)	306.76±68.03	379.64±151.00	346.11±132.92	0.009	S
S. Al. Amylase (u/l)	8.02±1.83	11.19±1.16	12.88±1.94	0.02	S

Keys: LH = Luteinizing Hormone; FSH = Follicle Stimulating Hormone; S = Salivary

Table 3 shows the multiple comparisons of the different gonadotropin state and the Control Group. The LH, FSH, prolactin and Salivary cortisol level in the control were significantly different from those of normogonadotropic

group (p<0.05) and hypergonadotropic group (p<0.05); there were equally significant difference (p<0.05) between the level of LH, FSH, Prolactin and Salivary cortisol in normogonadotropic group and hypergonadotropic group. 52 (63.4%) of the 82 female cases studied were of normal prolactin state against 30 (36.6%) that were hyperprolactinaemia state as shown in Table 7.

There was statistically significant difference (p<0.05) in the hormones and biomarkers measured across control group, normal prolactin group and hyperprolactinaemia group, except in progesterone no statistically significant differences (p>0.05) as shown in Table 4. The mean FSH of the study group (4.50±2.20 miu/ml) was statistically lower (p<0.05) than the control group (5.91±1.66 miu/ml); mean LH of the study group (5.64±2.26 miu/ml l) show no statistical significant difference (p>0.05) to that of the control group (5.43±1.66 miu/ml); mean Prolactin of the study group (18.01±11.56 ng/ml l) was statistically higher (p<0.05) than the control group (6.98±3.34 ng/ml).

Table 4: Comparison of hormones and biomarkers according to prolactin state in the female category.

Variables	Study group			p-value	Sig
	Control Mean±sd N=50	Normoprolactin state Mean±sd N=52(63.4%)	Hyperprolactinaemia Mean±sd N=30(36.6%)		
LH (miu/ml)	8.88±1.96	12.12±16.04	9.07±6.34	0.007	S
FSH (miu/ml)	12.03±14.71	13.22±15.48	10.00±13.29	0.01	S
Prolactin (ng/ml)	8.59±3.36	18.55±29.16	33.07±15.83	0.0001	S
Progesterone (ng/ml)	8.48±3.59	6.56±5.01	6.37±5.49	0.053	Ns
Estrogen (pg/ml)	73.84±21.46	60.90±18.57	54.50±20.31	0.0001	S
S. Cortisol (micromole/l)	306.76±68.03	304.94±117.75	489.17±119.33	0.0001	S
S. Al. Amylase(u/l)	8.02±1.83	9.71±9.93	14.85±6.43	0.0001	S

Keys: LH = Luteinizing Hormone; FSH = Follicle Stimulating Hormone; S = Salivary

Table 5: Mean hormones, biomarkers and sperm quality in the study and control group in the males category.

Parameter	Study group Mean±s.d (82)	Control group Mean±s.d (50)	Normal value	p-value
FSH (miu/ml)	4.50±2.20	5.91±1.66	2.0-14.0	<0.001
LH (miu/ml)	5.64±2.26	5.43±1.66	2.0-14.0	0.560
Prolactin (ng/ml)	18.01±11.56	6.98±3.34	4.0-12.0	<0.001
Testosterone(ng/ml)	3.44±2.35	5.86±1.55	2.5-10.0	<0.001
S. Cortisol(micromole/l)	449.75±106.81	340.65±72.53	221-552	<0.001
S. Amylase (u/l)	13.12±4.39	8.45±3.01	1-15	<0.001
Sperm cells count ($x10^6$)	19.42±26.08	53.80±11.74	>20 $x10^6$	<0.001
Sperm cells active (%)	33.99±26.07	49.10±14.80	>50%	<0.001
Viability (%)	60.7±13.12.9	74.8±14.71	-4.712	<0.001
Semen volume (ml)	3.25±1.97	5.62±2.0	-6.077	<0.001

Keys: LH = Luteinizing Hormone; FSH = Follicle Stimulating Hormone; S = Salivary

Table 6: Comparison of hormones and biomarkers according to semen quality of the male category.

Variables	Study group				p-value	Sig
	Control Mean±sd N=50	Normospermia mean±sd N=54(65.9%)	Oligospermia mean±sd N=15(18.3%)	Azoospermia mean±sd N=13(15.8%)		
FSH (miu/ml)	5.91±1.66	5.53±1.96	3.22±0.87	1.80±0.48	0.0001	S
LH (miu/ml)	5.43±1.66	6.46±1.97	5.12±2.03	2.90±1.01	0.0001	S
Prolactin(ng/ml)	6.98±3.34	12.94±6.05	18.82±7.50	37.73±11.45	0.0001	S
Testosterone (ng/ml)	5.86±1.55	5.75±1.65	2.73±0.81	1.04±0.75	0.0001	S
S. Cortisol (micromole/l)	340.65±72.53	397.5±79.95	505.33±73.76	598.46±46.52	0.0001	S
S. Amylase (u/l)	8.45±3.01	11.19±2.94	14.13±3.20	19.85±3.53	0.0001	S
Sperm cells count ($x10^6$)	53.80±11.74	46.40±19.43	5.73±3.41	0.00±0.00	0.0001	S
Sperm cells active (%)	49.10±14.80	48.92±18.97	10.67±6.78	0.00±0.00	0.0001	S

Keys: LH = Luteinizing Hormone; FSH = Follicle Stimulating Hormone; S = Salivary

Table 7: Correlation between hormones and biomarker in hypergonadotropic hypogonadism group of the females category.

Correlation	R-value	p-value
LH and FSH in hypergonadotropic	0.651	0.003
LH and prolactin in hypergonadotropic	-0.009	0.972
LH and progesterone in hypergonadotropic	-0.472	0.048
LH and estrogen hypergonadotropic	-0.329	0.183
LH and s. Cortisol in hypergonadotropic	-0.041	0.873
LH and s. Al. Amylase in hypergonadotropic	0.059	0.815
FSH and prolactin in hypergonadotropic	0.187	0.457
FSH and progesterone in hypergonadotropic	-0.310	0.210
FSH and estrogen in hypergonadotropic	-0.273	0.273
FSH and s. Cortisol in hypergonadotropic	0.072	0.776
FSH and s. Al. Amylase in hypergonadotropic	0.229	0.362
Progesterone and prolactin in hypergonadotropic	-0.324	0.190
Progesterone and estrogen in hypergonadotropic	0.587	0.010
Progesterone and s. Cortisol in hypergonadotropic	-0.300	0.226
Progesterone and s. Al. Amylase in hypergonadotropic	-0.368	0.133
Prolactin and estrogen in hypergonadotropic	0.111	0.662
Prolactin and s. Cortisol in hypergonadotropic	0.818	0.0001
Prolactin and s. Al. Amylase in hypergonadotropic	0.892	0.0001
Estrogen and s. Cortisol in hypergonadotropic	0.042	.0867
Estrogen and s. Al. Amylase in hypergonadotropic	0.082	.0746
S. Cortisol and s. Al. Amylase in hypergonadotropic	0.907	0.0001

Keys: LH = Luteinizing Hormone; FSH = Follicle Stimulating Hormone; S = Salivary

Table 8: Correlation between hormones, biomarker and semen quality in oligospermia group of the males category.

Correlation	R-value	p-value
LH and FSH in oligospermia	0.529	0.042
LH and prolactin in oligospermia	-0.269	0.332
LH and testosterone in oligospermia	0.054	0.848
LH and s. Cortisol in oligospermia	0.103	0.716
LH and s. Al. Amylase in oligospermia	-0.080	0.776
LH and sperm cells count in oligospermia	-0.015	0.957
LH and sperm cells active in the oligospermia	-0.007	0.982
FSH and prolactin in oligospermia	-0.542	0.037
FSH and testosterone in oligospermia	0.616	0.015
FSH and s. Cortisol in oligospermia	-0.351	0.200
FSH and s. Al. Amylase in oligospermia	-0.543	0.037
FSH and sperm cells count in oligospermia	0.679	0.005
FSH and sperm cells active in the oligospermia	0.311	0.260
Prolactin and testosterone in oligospermia	-0.338	0.219
Prolactin and s. Cortisol in oligospermia	0.497	0.060
Prolactin and s. Al. Amylase in oligospermia	0.519	0.048
Prolactin and sperm cells count in oligospermia	-0.476	0.073
Prolactin and sperm cells active in the n oligospermia	-0.268	0.335
Testosterone and s. Cortisol in oligospermia	-0.241	0.386
Testosterone and s. Al. Amylase in oligospermia	-0.553	0.033
Testosterone and sperm cells count in oligospermia	0.552	0.033
Testosterone and sperm cells active in the oligospermia	0.572	0.026
S. Cortisol and s. Al. Amylase in oligospermia	0.492	0.062
S. Cortisol and sperm cells count in n oligospermia	-0.485	0.067
S. Cortisol and sperm cells active in the oligospermia	-0.450	0.092
S. Al. Amylase and sperm cells count in oligospermia	-0.585	0.022
S. Al. Amylase and sperm cells active in the oligospermia	-0.383	0.159
Sperm cells count and sperm cells active in the oligospermia	0.317	0.249

Keys: LH = Luteinizing Hormone; FSH = Follicle Stimulating Hormone; S = Salivary

Table 9: Correlation between hormones, biomarker and semen quality in azoospermia group of the male category.

Correlation	R-value	p-value
LH and FSH in azoospermia	0.083	0.788
LH and prolactin in azoospermia	-0.244	0.422
LH and testosterone in azoospermia	-0.090	0.771
LH and s. Cortisol in azoospermia	-0.136	0.657
LH and s. Al. Amylase in azoospermia	-0.533	0.061
FSH and prolactin in azoospermia	-0.083	0.788
FSH and testosterone in azoospermia	0.024	0.939
FSH and s. Cortisol in azoospermia	0.041	0.895
FSH and s. Al. Amylase in azoospermia	-0.014	0.964
Prolactin and testosterone in azoospermia	-0.542	0.056
Prolactin and s. Cortisol in azoospermia	0.258	0.395
Prolactin and s. Al. Amylase in azoospermia	0.407	0.168
Testosterone and s. Cortisol in azoospermia	-0.213	0.486
Testosterone and s. Al. Amylase in azoospermia	-0.348	0.243
S. Cortisol and s. Al. Amylase in azoospermia	-0.607	0.028

Keys: LH = Luteinizing Hormone; FSH = Follicle Stimulating Hormone; S = Salivary

The testosterone in the study group (3.44±2.35 ng/ml) was significantly lower ($p<0.05$) than the control group (5.86±1.55ng/ml); the Salivary cortisol was significantly higher ($p<0.05$) in the study group (449.75±106.81) compared to the control group (340.65±72.53). Salivary Alpha Amylase was significantly higher ($p<0.05$) in the study group (13.12±4.39) compared with the control group (8.45±3.01); the Sperm cell count (x106) was significantly lower ($p<0.05$) in the study group (31.42±26.08 cells/ml) compared with that of control group (53.80±11.74 cells/ml); the percentage of active Sperm cells (%) was significantly lower ($p<0.05$) in the study group (33.99±26.07) compared with the control group (49.10±14.80) as shown in table 5. The mean ejaculate volume was also higher in the control group ($p<0.05$) compared with the study group, 5.6 ml versus 3.3 ml.

Of the 82 male cases examined, 54(65.9%) were normospermia, 15(18.3%) were Oligospermia while 13(15.8%) were Azoospermia as shown in table 4.6. There was statistically significant difference ($p<0.05$) in the hormones, biomarkers and semen quality measured across control group, normospermia, Oligospermia and Azoospermia group respectively as shown in table 6.

In hypergonadotropic state, a strong significant positive correlation was found between LH and FSH ($r=0.651$, $p<0.05$), a strong significant positive correlation was seen between progesterone and estrogen ($r=0.587$, $p<0.05$), a very strong significant positive correlation was seen between prolactin and serum cortisol ($r=0.818$, $p<0.05$) and serum amylase ($r=0.892$, $r<0.05$) also a very strong significant positive correlation was seen between salivary cortisol and salivary alpha amylase ($r=0.907$, $p<0.05$) as shown in table 7.

In the Oligospermia category, there was a strong significant positive correlation between LH and FSH ($r=0.529$, $p<0.05$), There was significant correlation between FSH and all the other parameters including the semen quality, except in cortisol ($r= -0.351$, $p>0.05$) and active sperm cells ($r= 0.311$, $p>0.05$), a strong significant positive correlation was found between testosterone and sperm cell count ($r=0.552$, $p<0.05$) and active sperm cell ($r=0.572$, $p<0.05$) as shown in table 8.

In the Azoospermia category, no significant correlation was found among the hormones, except a strong significant negative correlation that was found between salivary cortisol and salivary alpha amylase ($r= -0.607$, $p<0.05$) as shown in table 9.

DISCUSSION

Infertility remains a major issue for many couples of childbearing age (15-45 years). The mean age of the study participants in the study group (32.00±4.2) years, investigated in FCT, Abuja, North Central Nigeria in this research is in tandem with (34.5±6.5) years reported by for infertile women investigated in Shagamu, South-Western Nigeria.[14] Fertility in couple is at its maximum in the mid- twenties and declines after the age of 27- 30 years.[15,16] Asserted or opined that fertility is halved in couple who are 35 years or above and declines sharply after the age of 37 years. The mean duration (time/period) of infertility among couples investigated in this research was 4.0 years; this result agrees with the work of, who reported a mean duration of infertility among women to be 5.0 years in Bida, North-Central Nigeria.[17] Some couples defer investigation after one or two years of unprotected sexual intercourse; however, it is essential that early investigation be started in couples of child bearing age. According to, it is customary for many

couples to defer investigation until after one year of unprotected sexual intercourse, but however, it is important to start early investigation, after six months of unprotected sexual intercourse in couples above 30 years, observed that 46% of couples in developing countries sought medical attention or evaluation for infertility before waiting two and half years, while over two third in developed countries had been trying to conceive for more than two and half years.[14-17]

The mean serum Prolactin value was significantly higher ($p<0.05$) in the study group compared with that of the control group. While the serum FSH, Progesterone, E2 where significantly lower ($p<0.05$) in the female study group when compared with that of the control group and no statistical difference in LH between the study group and control group ($p>0.05$); Serum FSH, Progesterone and E2 were significantly lower because as envisaged, infertility must have induced chronic stress that directly shuts off all non-essential systems and has effect on hypothalamus - pituitary - gonadal axis that regulates fertility hormones secretion; this findings agree with, who recorded high level of Prolactin in infertile couples.[18] It was observed that about 36.6% of the women with infertility investigated in this study have hyperprolactinemia. The result of hyperprolactinemia in this study is quite different from the findings earlier reported by previous studies; recorded 48% Cases of hyperprolactinemia among the 98 infertile women with hormonal abnormality.[17,19] Asserted that hyperprolactinemia has been implicated to interfere with ovulation leading to infertility; this includes decrease of Gonadotropin Releasing Hormone (GnRH), inhibition of LH and FSH releases or effects of both Oestrogen and Progesterone secretion in the ovary. Both LH and FSH are needed for follicular development and estrogen production, hence low levels of these hormones may mean that fewer numbers of follicles will develop and there will be no Graffian follicle formation.[20]

It has also been reported that hyperprolactinemia and low levels of LH, FSH and Progesterone may cause anovulation and hence infertility, also that typically, female with hyperprolactinemia will present with anovulation (lack of ovulation), amenorrhea (no menstruation) and sometimes galactorrhea (abnormal milk production).[14] In this study, there were conditions of hypogonadotropic hypogonadism and hypergonadotropic hypogonadism where the LH, FSH and the Progesterone were statistically lower ($p<0.05$) when compared with the control group; these suggest the condition of hypogonadotropic hypogonadism, where there is no ovulation due to low levels of LH and FSH; these may be as a result of dysfunction of the hypothalamus or the pituitary gland in the women and as consequence, are unable to secret adequate gonadotropins to stimulate the ovary; some causes of this condition genetically are: cerebral infection or radiation, cerebral tumor, kallmans syndrome i.e. the deficiency of gonadotropic releasing hormone, stress and malnutrition. In this study, 6 subjects in the female study group (7.3 %) shows hypergonadotropic hypogonadism, a condition where the LH and FSH levels are high and the progesterone level is low, progesterone appears to play key role in fertility by it preserving the fertilized ovum after implantation in the uterus; this role cannot be played in the condition of low progesterone level, which can lead to miscarriage in the expected mother.[14] The finding in this study further shows that there was 7.3% occurrence of hypergonadotropic hypogonadism among the study group; this is considered to be lower than 13.3% reported by.[14]

It is observed in this research that 34.1% of the male in the study group presented with low Serum FSH and Testosterone levels, low Sperm cells count and low Active sperm cells (%), ($p<0.05$) relative to the control group; this findings agrees with the report of, who reported low sperm quality, low sperm quantity and hormonal imbalance as causes of infertility in male in couples of child bearing age.[22] The sperm count in this study is categorized into normospermia (normal sperm cell count), oligospermia (low sperm cell count) and azoospermia (no sperm cell); and 18.3% of the male study subjects presents with the condition of oligospermia while 15.8% presents with azospermia; also reported hormonal abnormalities in male infertility in Kano, Nigeria in both oligospermia and azospermia.[23] Also reported that abnormal Testosterone and FSH levels can impair the mechanisms of spermatogenesis; furthermore, low Testosterone concentration is a marker of HPA activation, one factor that can deregulate Testosterone and FSH secretion is chronic anxiety and depression.[24] In men, stress adversely affect semen quality and can inhibit GnRH secretion through H-P-axis activation; stress-induced spermatogenesis impairment is typically manifested in decreased sperm count and motility and increased percentage of morphologically abnormal sperm.[25] An increase in stress hormone levels i.e. cortisol can impair androstenedione to testosterone conversion in the Leydig cells. This disrupts the hormonal transformation cycle required for testosterone secretion, leading to lower average values of semen volume and sperm quality.[26]

However, there is a statistically significant difference in the values of prolactin ($p<0.05$) in the male study group relative to the control group, this finding agrees with that of, who reported high Prolactin concentration in the males with infertility.[27] The findings in this study suggest that most of the infertility cases experienced by couples, about 35%-40% could be attributed to the male subjects; this is due to the fact that without a viable active sperm cells during the process of sexual intercourse, there will be no fertilization of the ovum, resulting in infertility.

In this study, the mean concentration of both biomarkers were significantly higher in the study group compared with the control group ($p<0.05$); although the values were within the upper limit of normal. However, in the male study subjects 13 (15.8%) with Azospermic condition, the biomarkers were significantly higher ($p<0.05$) compared with the normospermic and oligospermic

conditions. The findings in this study support the reports of who reported high Cortisol as the adverse effect of stress on infertility, and opined that 30% cases of infertility are attributed to stress; that when stress reducing measures are applied, those couples who could not get pregnant before got pregnant.[13,28] This result confirms the impacts of stress on sperm quality, in line with those reported by other authors.[29-31] Although, some researchers have disclaimed the effect of stress on fertility, could not see any obvious link of stress and infertility.[32] However, the elevated values of biomarkers in this study suggest and support the adverse negative impact of stress on fertility in couples of child bearing age as also reported by, that male patients with anxiety and depression were found to have lower testosterone levels and low sperm quality.[31] Thus, stress can compromise every aspect of fertility including libido, sperm quality, ovulatory capacity, and implantation.[33] High cortisol level in this study suggests an indication of chronic stress; where the stress neuroendocrine are stimulated via the hypothalamus- pituitary - adrenal axis, which in turn affects the activities of the Gonadotrophic Releasing Hormones (GnRH). The stress hormones inhibit and decrease the pulsatility of the GnRH which is responsible for the stimulation and production of the gonadotropins (FSH and LH), these suggest the reason for low values of FSH, E2, Testosterone and Progesterone obtained in this study. Various levels of correlations were observed between the biomarkers and infertility conditions; in hypergonadotropic, hyperprolactinaemia, Oligospermia and Azospermia states, a strong significant positive correlation was found between the hormones and the stress biomarkers.

CONCLUSION

The findings of this study suggest that multiple endocrine disorders exist in some cases of infertility and that hormonal abnormalities, sperm abnormalities and elevated stress biomarkers may among other conditions be responsible for some cases of infertility among couples within reproductive age. Hormones, sperm analysis and stress biomarkers evaluation should therefore be part of routine investigation of infertile couples in Nigeria; these results should be used in conjunction with patient's history and clinical examination.

ACKNOWLEDGEMENTS

Authors sincerely appreciate the Management and staffs of the various General Hospitals in Federal Capital Territory, Abuja for allowing us use their facilities for the collection of samples from the study participants; also very thankful to Alpha Royal Medicals Ltd for allowing us access to use their facilities for all the analytical work.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Abriba SP, Osadolor HB. Evaluation of hormonal profile and some stress biomarkers in infertile couples in Abuja, Nigeria. Int J Res Med Sci 2020;8:1514-22.