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Serum and seminal plasma hormonal profiles of infertile Nigerian male

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Summary

Male infertility constitutes a worldwide problem, especially in Nigeria where most men do not readily accept that they may contribute to the couple's infertility. In order to assess hormonal disturbances in the male infertility we compared male reproductive hormonal levels in human serum and seminal plasma and evaluated the hypothalamic-pituitary-testicular-axis in infertile Nigerian males. The biophysical semen parameters were assessed by W.H.O. standard manual method. Serum and seminal plasma male reproductive hormones (Leutinizing hormones, Follicular stimulating hormone, Prolactin and Testosterone) were measured by Enzyme Immunoassay (EIA) technique of W.H.O. in sixty (60) infertile adult male Nigerians (Oligospermic; n = 40 and azoopermic; n = 20) and forty controls of proven fertility (Normospermic subjects; n = 40). The results show that the serum concentrations of gonadotropins (LH and FSH) were significantly higher ($P<0.05$) in infertile subjects than controls. Patterns of serum prolactin levels were similar. The values of gonadotropins in serum were significantly higher ($P<0.05$) than those of seminal plasma. Seminal plasma testosterone in infertile subjects was significantly higher ($P<0.005$) than that of controls but the serum levels of testosterone were significantly higher($P<0.05$) in azoospermic than oligospermic subjects and controls. There was no significant correlation between serum hormonal level and seminal plasma hormonal level in all the groups($P<0.05$). We concluded that male infertility in Nigerians is characterized by hyperprolactinaemia, raised serum gonadotropins (LH, FSH), and raised seminal plasma testosterone. Hormonal profiles in serum and seminal plasma were not significantly correlated, and hence cannot be used as exclusive alternative in male infertility investigations. The observed spermogram in spite of significant elevation of seminal plasma testosterone in infertile males investigated suggests Sertoli cells malfunction.

Keywords: - *Serum, seminal plasma, reproductive hormones, male infertility.*

Résumé

L'infertilité masculine constitue un problème mondiale spécialement au Nigeria ou la plupart des hommes n'acceptent pas directement qu'ils peuvent contribuer à l'infertilité du couple. Pour évaluer les perturbations hormonales chez les hommes infertile, nous avons comparé le taux des hormones reproductrice male dans le sérum humain, le plasma séminal et l'axe hypothalamique-pituitaire-testiculaire. Ces paramètres biophysiques du sperme étaient évalués par la méthode standard de l'OMS. Les hormones reproductrice male dans le sérum et le plasma séminal (LH, FSH, Prolactine et testostérone) étaient mesurées par la technique enzymatique de l'OMS chez 60 adultes male infertile (Sujets oligospermique n=40, Azoospermie n=20) et 40 hommes sains et fertile (sujets normospermique n=40). Les résultats démontraient que les concentrations du sérum en gonadotrophines étaient significativement plus élevées ($P<0.05$) aux sujets infertile qu'aux individus sain. La fréquence de la prolactine en sérum était semblable chez les deux groupes. Les valeurs gonadotrophines en sérum étaient significativement plus élevées que dans le plasma séminal. La testostérone en plasma séminal chez les sujets était significativement plus élevée qu individus sains mais les taux de testostérone étaient significativement plus élevés aux azoospermies qu'aux oligospermies et aux contrôles. Il n'avait pas de corrélation entre le taux du sérum et plasma séminal hormonal chez tous les groupes et ne peut pas être utilisé en investigation des infertilité chez les males. Nous avons conclu que l'infertilité chez les adultes males nigérian est caractérisée par l'hyperprolactinemie, une élévation des taux des gonadotrophines en sérum et une élévation du taux de testostérone en plasma séminal. Le spermogramme des males investigués suggérait un mal fonctionnement des cellules de Sertoli.

Introduction

Involuntary infertility is a world wide problem the frequency of which varies from one area to another. Until recently, little attention has been placed on male contribution to infertility in the couple due to the general erroneous belief that infertility is a female problem most especially in Africa. The World Health Organization (WHO) in 1992 [1] suggested that the male factor could be responsible for up to 33.3% of cases, female factor for 25%, both male and female factors for 20% and in 15% of cases no detectable cause would be found. Generally, it is believed that about 5% of all couples are infertile for complex reasons, which are difficult to identify and for which present day treatment is largely ineffective [2].

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Reports in the past have shown no specific trend in the serum hormone profiles of infertile males [3 – 4]. Among infertile men, Chahral and Mechan [5] reported normal levels of gonadotropins and gonadotropin releasing hormone (GnRH) response while Chaltovaj and Walts [4] reported increases in the basal levels of gonadotropins and a low testosterone level. Swerdloff *et al* [3] showed that hyperprolactinaemia occurred in males with hypogonadism without any abnormality in estrogen level. Therefore, it was concluded that unless the evidence of androgen deficiency occurs assessing endocrine function in infertile males is generally unhelpful. Seminal fluid is an important transport medium for spermatozoa through the epididymis, vas deferens and urethra into the vagina. Hence major changes in the constituents of the seminal fluid could produce abnormal sperm functional capabilities. Since all these hormones are detectable in the seminal fluid in various measurable quantities it is possible that estimation of these hormones in the seminal fluid may be helpful in the assessment of male infertility. This idea forms the basis of this study, which was designed to determine the correlation between seminal plasma and serum hormones levels in both fertile and infertile males in order to assess the relationship between seminal plasma hormones level and male infertility.

Materials and methods

Subjects

All consenting males in infertile relationship attending infertility clinics of the Department of Obstetrics and Gynaecology and Urology Clinic, Department of Surgery, University College Hospital, Ibadan, Nigeria, within the period of study (February 1998 – November 2001) and that met the selection criteria were recruited into the study. Inclusion and exclusion criteria for selection of subjects are as follows:

Inclusion Criteria

- Men within reproductive age of 20 – 45 years
- Male partners of couples in good marital harmony, living together and having regular unprotected coitus for 2 or more years
- Normal distended testes.

Exclusion Criteria

- Male contraceptive users
- Testicular varicecoele
- Genital infections
- Long term medications
- Previous groin/scrotal surgery
- Known HIV positive men
- Heavy smoking/chronic alcohol intake
- Chronic and serious systemic illness

Men currently on fertility drugs or steroid preparations

The control subjects were recruited mainly from semen donors for intra – uterine-fertilization and male partners of pregnant women and nursing mothers attending the Antenatal Clinic of the Department of Obstetrics and Gynaecology, University College Hospital (U.C.H) Ibadan. The controls were recruited from a similar population as that used in the selection of cases. They have similar demographic characteristics (Table 1). A normal seminal fluid analysis with sperm count >20million/cm^3 (Normospermia) and having at least two living children were used as criteria for selecting control subject in addition to the exclusion criteria used in the selection of cases.

All the subjects gave informed consent for participating in the study. The study received the approval of the Ethical Committee of the College of Medicine University of Ibadan and University College Hospital Ibadan. On the first visit to the clinic, a complete medical history was obtained and a physical examination was performed for each subject. This includes measurement of body weight, height, and systolic and diastolic blood pressures.

The study design included three groups based on their sperm count: Group 1 consisted of male partners of infertile couples with sperm count less than 20 million/cm^3 (Oligospermia; n = 40); Group 2 consisted of male partners of infertile couples with no spermatozoa in their semen (Azoospermia; n = 20) and Group 3 consisted of healthy fertile control males with sperm count greater than 20 million/cm^3 (Normospermia; n = 40). Male partners of infertile couple with sperm count greater than 20million/cm^3 (Normospermia) were regarded as sub fertile and hence excluded from this study.

Biophysical analysis of semen samples

Semen sample was collected from each subject on two occasions, two weeks apart, after at least 3 days but not more than 6 days periods of abstinence by masturbation without a lubricant or soap into a pre – warmed clean wide mouth sterile container in a private room near the laboratory. Semen analysis was performed according to the guidelines of W.H.O in the manual for examination of human semen and semen – cervical mucus interaction [1].

Hormones assays

About 10mls of venous blood was collected from the antecubital vein of each subject into plain bottles between 8.00 and 9.00 am after overnight fasting. After clot retraction, the samples (sera and semen) were centrifuged at 3,000 rpm for 10 minutes. The plasma was later collected and stored at –20°C until analyzed; it was assayed in small aliquots so that it was thawed only once. The hormone assays were carried out using enzyme immunoassay technique developed for the special program research in human reproduction by the W.H.O [6].

Statistical analysis

The Statistical Package of Science and Social Sciences

Table 1: Admission characteristics of the three groups of subjects

Indices	Control (N=40)	Case I (N=40)	Case II (N=20)	P-value
Age (years)	36.6 (35.02-38.08)	35.6 (32.76-37.34)	35.2 (31.76-36.42)	P>0.05
Weight (kg)	63 (62.54-69.76)	69 (65.09-74.71)	68 (72.18-77.82)	P>0.05
Height (m)	5.71 (5.61 - 5.81)	5.74 (5.60 - 5.88)	5.56 (5.42 - 5.69)	P>0.05
Systolic pressure (Hgm)	129.67 (123.50-134.30)	133 (126.32-136.68)	122.73 (117.34-128.07)	P>0.05
Diastolic pressure (Hgm)	85.33 (81.13 - 87.37)	83.75 (81.17 - 87.83)	78.64 (74.65 - 82-62)	P>0.05
Temperature (Axilla; 0°)	36.40 (36.27 - 36.49)	36.42 (36.31 - 36.52)	36.40 (36.29 -36.51)	P>0.05

Values expressed as mean (95%) Confidence Interval)

(SPSS) software was used for the statistical analysis. Sperm biophysical characteristic did not exhibit normal distributions in large groups of adult males [7-9]. This was the case among the 100 men studied (as determined by Wilk's test). The best transformation of the data that yielded normal distributions for each of the variables without normal distribution was the logarithmic (base 10) transformation.

The results were assessed using Kruskal Wallis Test both between group and within group comparison, the latter to ensure that the effect of between subjects variations was removed. Comparison between two groups was further analysed with Mann -Whitney U test. Relationships between the investigated parameters were established using Pearson's correlation.

Results

The admission characteristics of the three groups of subjects shown in table 1 were similar. Table 2 shows that the gonadotropins and prolactin levels were significantly higher in the serum than in seminal plasma while the reverse was the case with testosterone in the infertile groups. No significant difference was seen in the fertile group. The serum gonadotropins and prolactin levels were significantly raised in the oligospermic and azoospermic males compared to controls while the serum testosterone was only significantly raised in the azoospermic males. No significant difference occurred in the seminal plasma levels of these hormones except testosterone levels, which was similar in the oligospermic and azoospermic males but significantly higher in these two groups than in the normospermic ones. The ratios of LH, FSH, PRL and T, levels in the serum to their seminal plasma levels were respectively 39:1, 33:1, 6:1 and 2:1 in controls, 26:1, 31:1, 4:1 and 1:2 in oligospermic males and 33:1, 12:1, 5:1 and 1:1 in azoospermic males.

Table 2: Comparisons of hormone levels in cases and controls

Hormones	Control	Oligospermia	Azoospermia
serum			
LH (i.u/L)	8.60 (7.87-9.89)	13.04*a (10.97-15.4)	13.90*a (9.37-22.82)
FSH (i.u/L)	8.44 (7.71-9.98)	25.60*a (19.99-32.72)	30.94*a (18.61-32.77)
PRO (mi.u/L)	246.40 (208.63-296.711)	426.50*a (346.03-572.32)	465.27*a (354.04-585.75)
TEST(i.u/L)	5.92 (4.91-6.61)	6.70*a (5.27-7.01)	20.27*+a (14.39-32.13)
Seminal Plasma			
LH(i.u/L)	0.22 (0.16-0.34)	0.50 (0.01-0.60)	0.42 (0.03-0.95)
FSH(i.u/L)	0.26 (022-0.31)	0.81 (0.37-0.89)	0.42 (037-0.49)
PROL(mi.u/L)	97.85 (87.27-107.62)	112.40 (93.27-144.12)	88.73 (70.59-111.95)
Test(i.u/L)	4.02 (3.99-4.51	14.62*b (12.06-8-18.71)	14.63*b (13.59-15.48)

Value expressed as Mean (95% confidence interval)
** Significant difference (Mann-Whitney Test)*
+Significant difference (Mann-Whitney Test)

As shown in Table 3, the serum FSH levels show significant inverse correlation with all semen biophysical parameters except volume while the serum LH correlated inversely with only sperm motility and morphology. Significant inverse correlation was also detected between serum prolactin and sperm motility and, between serum testosterone and sperm viability and morphology. Among the seminal plasma hormones only the testosterone level had significant inverse correlation with the sperm count, motility, viability and morphology.

Table 3: Pearson's correlation coefficient (R) between semen biophysical parameters and hormonal levels

Semen	Serum				Seminal plasma			
	LH	FSH	Prol	Test	LH	FSH	Prol.	Test
Volume	+0.66	+0.05	+0.04	+0.04	+0.12	+0.29[a]	+0.09	+0.01
Sperm count	-0.38[a]	-0.45[a]	-0.22	-0.12	-0.09	-0.19	-0.01	-0.54[a]
Motility	+0.29[a]	-0.45[a]	-0.38[a]	-0.28	+0.03	-0.24	+0.15	-0.46[a]
Mean progressive motility	-0.34[a]	0-0.45[a]	-0.32	-0.23	-0.03	-0.24	+0.10	-0.45
Viability	-0.23	-0.41[a]	-0.26	-0.35[a]	-0.02	-0.25	+0.13	-0.37[a]
Morphology	-0.34[a]	-0.44[a]	-0.19	-0.34[a]	+0.0	-0.27	-0.14	-0.39

No significant correlation was observed between the levels of the hormones in the serum and seminal plasma (Table 4), except for serum testosterone, which shows positive correlation with seminal plasma prolactin.

Table 4: Pearson's correlation coefficient (R) between serum and seminal plasma hormonal levels in all subjects

	Seminal plasma			
	LH	FSH	PROL	TEST
Serum				
LH	+0.05	-0.02	-0.09	-0.13
FSH	-0.08	-0.11	+0.11	-0.11
PROL	-0.02	-0.04	-0.20	-0.10
TEST	+0.28	+0.21	+0.33a	+0.21

Discussion.

In normal subjects, the Leuteinizing hormone (LH) secreted in the pituitary gland as a result of the stimulatory effect of hypothalamic gonadotropin releasing hormones (GnRh) on the gland blinds to receptor sites in the testes to cause testosterone production by various enzymatic reactions at the cellular level [10]. This testosterone exerts a negative feedback effect on the receptor sites in the hypothalamic – pituitary complex thus regulating its own production. Apart from its effect on testosterone production, LH is also important for spermatogenesis [10,11]. The follicular stimulating hormone (FSH), also produced in the pituitary gland by the stimulatory effect of GnRh, binds to specific receptors in the Sertoli cells of the testes to cause the production of androgen binding protein (ABP) which binds to testosterone and concentrate it in the seminiferous tubules for spermatozoa production and maturation. FSH also causes the production of inhibin in the testes that acts on the pituitary gland to inhibit its own production. The serum level of inhibin in adult male is inversely proportional to the level of serum FSH but not LH or testosterone [12]. In addition, to inhibiting FSH production in the pituitary gland, the locally produced inhibin in the testis may play a role in paracrine regulation of testicular function. When these processes are in good working order, normal spermatogenesis and hence male fertility ensures. In this study, azoospermia in a group of our subjects suggests an absence of spermatogenesis rather than an obstruction to sperm release from the testes. This is because of the significantly raised serum FSH level (more than twice normal level), which indicates nonuse of this hormone despite its continuous secretion by the pituitary gland. This may be due to either receptor binding failure or degeneration of sertoli cells or seminiferous tubules that harbour the sertoli cells. Various studies have demonstrated an association between destruction of germinal epithelium and elevated FSH levels [13 – 14. The high serum testosterone levels in our study groups indicated an adequate stimulatory effect of LH on the Leydig cells, but the probably poor production of ABP by the Sertoli cells in response to FSH stimulation prevents the binding of testosterone for spermatogenesis, resulting in the accumulation of this free steroid hormone in the testis and blood. The raised FSH suggests that serum inhibin function is at the lowest ebb. It therefore, reflects a paucity of inhibin production in the testis since this glycoprotein (inhibin) is a good marker of testicular function, which may be used in the diagnosis of patients with complete absence of spermatogenesis [12, 16].

The lack of correlation between serum and seminal plasma gonadotropins levels suggests that the mechanism for the secretion of these hormones into blood and seminal plasma are different. However, the strong positive correlations between the serum levels of FSH and LH and between their levels in the seminal plasma suggest that the two hormones are similarly concentrated in these two compartments. The two gonadotropins are similar in molecular structures with very little difference, and are both capable of binding to the 400AAS extra – cellular hormone – binding domain of LH receptor sites of the Leydig cells and stimulate testosterone secretion. The competitive binding of elevated serum FSH to LH receptor will explain the elevation of serum LH levels in the infertile groups despite the elevated serum testosterone level. Therefore,

results from this study suggest that in male infertility, degeneration of seminiferous tubules and/or sertoli cells occurs and, results in loss of negative feedback mechanism and extensive production of hormones that are unutilized. Hence these hormones accumulate in blood. Oligospermic males unlike the azoospermic still have some functioning seminiferous tubules and/or sertoli cells that are able to utilize some of the testosterone produced by the testicular Leydig cells hence their serum testosterone level is similar to that of normospermic despite their significantly raised seminal plasma testosterone level. The little ABP produced in response to FSH stimulatory effect on the sertoli cells binds enough testosterone to prevent its accumulation in blood. On the other hand, the inhibin produced in the sertoli cells are possibly too low for a reasonable negative feedback mechanism, hence the accumulation of FSH in blood. Therefore, in assessing male infertility, measuring seminal plasma testosterone will be a better alternative to an estimation of serum testosterone. The differentiation between oligospermic males and the azoospermic ones can be made by estimating the serum testosterone level which is usually not raised in oligospermic males. Thus the ratio of serum testosterone to seminal plasma testosterone should give a clear differentiation between the two groups of infertile patients since this ratio is 1:2 in oligospermic males and 1:1 in azoospermic males. Similarly the ratio of serum FSH to seminal plasma FSH, which is 12:1 in azoospermic males in this study as against 31:1 in oligospermic males or 33:1 in those with normospermia, may be used to differentiate between the two groups of infertile subjects.

Our finding of a significantly raised serum gonadotropins levels in both infertile groups is in keeping with reports elsewhere [5,17]. It was observed in our study that FSH levels are particularly more increased than LH in the infertile subjects (ratio 2:1; Table 2). This is in keeping with reports by Hurley and Burger in 1984 [18]. Although these workers suggested that raised serum gonadotropins, especially FSH in the presence of normal or low serum testosterone is evident of a primary gonadal disorder, our finding of raised serum testosterone in azoospermic males will suggest that testicular testosterone production is not necessarily deficient in males with primary gonadal disorder, especially those without signs and symptoms or hypogonadism.

Although the role and mechanism by which hyperprolactinaemia affects male fertility is still unclear, our finding of significantly raised serum prolactin levels in infertile males compared to normospermic ones is in agreement with previous studies. [19,20]. A positive correlation observed in this study between seminal plasma prolactin and seminal plasma LH on one hand and also between serum prolactin and seminal plasma testosterone on the other are good evidence that prolactin interacts with these hormones along the hypothalamic – pituitary – testicular axis, and contributes to testicular spermatogenesis. Hyperprolactinaemia has been associated with hypogonadism in both human and animal studies [19,21. The mechanism of such interaction is unclear (20). It may be due to a defective inhibitory action of the poorly produced inhibin from the gonads on the hypothalamic – pituitary complex. However, hyperprolactinaemia was observed in this study in association with increased gonadotropins levels. A possible explanation for this is the competitive binding of prolactin with 400AS extra cellular hormone – binding domain of G – protein coupled receptors (LH receptor) resulting in accumulation of gonadotropins, especially LH in blood. Prolactin is also capable of binding with testosterone in the testes thereby making the steroid hormone inaccessible to ABP and resulting in its accumulation in seminal plasma, and possibly reduced spermatogenesis, hence the significantly high testosterone levels in the infertile subjects in this study. Other investigators have also reported an association between hyperprolactinaemia and oligospermia and azoospermia [20,22–24].

In conclusion, this study shows that hypergonadotropism, hyperprolactinaemia and increased seminal plasma testosterone levels are associated with male infertility in Nigerians. Appropriate interaction of these hormones, especially prolactin and gonadotropins, along the hypothalamic – pituitary – testicular - axis is important for normal spermatogenesis. Excess of these hormones in serum reduces sperm quantity and quality, and therefore, fertilization capacity, thus causing male infertility. An assessment of these hormones, especially its distribution between serum and seminal plasma (serum/seminal plasma ratio) and seminal plasma testosterone should be a useful diagnosis tool in investigating male infertility, especially in differentiating between males with oligospermia and azoospermia.

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