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Hormonal Status Assessment of Infertile Congolese Men

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Abstract

Background: The pathologies causing male infertility are various (congenital or acquired) and concern several hormone-producing organs: the hypothalamus, pituitary gland, testes and adrenals. The hormonal dosage includes systematically testosterone, FSH and LH. These analyses often highlight hypogonadism hypogonadotropic or hypergonadotropic. They can sometimes be normal. The present study aimed to establish the hormonal profile of infertile men residing in Brazzaville. **Patients and Methods:** It was a cross-sectional descriptive study during five years (from 2018 to 2023). It concerned 344 infertilemen with an abnormal spermogram and spermocytogram. The method was performed from the blood dosage of testosterone, FSH, and LH using the Elisa technique. **Results:** The hormonal assessment was not normal in 48.83% (168/344) of cases. Increased values of testosterone were noted in 6.10% of cases and decreased in 12.20%. Abnormal high values of FSH were observed in 14.24% of cases and decreased values in 8.13%. LH was elevated, *i.e.* 2.03% of cases and decreased in 6.10% of subjects. **Conclusions:** A hormonal disturbance was observed in almost half of the infertile men. It concerned the hypothalamus-pituitary and the testes axis and indicated mainly a state of hypogonadism with high FSH and low LH.

Keywords

Male infertility, Hormones, Testosterone, FSH, LH, Hypogonadism

1. Introduction

Male infertility is a disorder that affects 10 to 15% of couples worldwide [1] [2] [3]. Data from the literature show that the male part of infertility is involved in 20% - 30% of cases or even more in certain countries [4] [5] [6].

Infertility has multiple causes: i) acquired (*i.e.*, chronic infections, testicular tumors, alcoholism, smoking); ii) congenital (Kallmann syndrome, Klinefelter syndrome); iii) environmental and idiopathic (40% to 45% of cases) [7] [8]. All of these causes are at the origin of hormonal disturbances (which are the subject of our study) found in 2% to 5% of infertility cases [9]. However, in 50% of cases the hormonal profile of infertile male subjects is normal [9].

The organs producing male hormones involved in reproduction are composed primary of the hypothalamus, the pituitary gland, the testicles and secondarily the adrenal glands and adipose tissue [7]. The hormonal assessment usually includes the dosage of testosterone, FSH (follicle-stimulating hormone), LH (luteinizing hormone), estrogens, prolactin, inhibin B and anti-Müllerian hormone. These hormones make it possible to define the type of hypogonadism (hypogonadotropic or hypergonadotropic) [10] [11] [12] [13].

This work carried out as part of a global study on male infertility in Brazzaville, the main objective of which is to research the causes of infertility in men which necessarily include hormonal analyses.

2. Patients and Methods

This was a cross-sectional and descriptive study during five (5) years from 2018 to 2023. It was carried out in four centres specialized in human reproduction, described in a previous article [14]. Informed consent was obtained from each patient and the study was approved by the Ethics Committee of Congo (CERSSA), N°086-40/MERSIT/DGRST/CERSSA/-23.

2.1. Patients

The study sample size was non exhaustive. Three hundred and forty-four (344) infertile men of congolese origin were included in the study. They were selected based on the following criteria:

- men consulting in the care sites specialized in couple infertility with the wish to become father;
- couple with no pregnant after twelve months of unprotected sexual intercourses;
- abnormal spermogram and spermocytogram;
- men in childbearing age;
- patient with complete medical record;
- informed consent obtained from the patients.

Their blood samples (venous blood collected on a dry tube very early in the morning) made it possible to obtain the serums. The latters were immediately decanted and stored between 2 and 8˚C for rapid analyses and −20˚C for future analyses.

2.2. Methods

2.2.1. Medical Data

Age and medical information were collected on pre-established survey forms.

2.2.2. Hormonal Assessment

The main hormonal parameters studied were the levels of blood testosterone LH and FSH, using the Sandwich Elisa technique. The principle of that technique is based on the antigen-antibody reaction.

Three different hormonal kits (Calbiotech firm, life science company) were used: LH (ref. LH231F); FSH (ref. FS232F) and testosterone (ref. TE373S).

LH and FSH protocol was as follows: preparation of the 1X wash buffer and placement of the wells in the LH (or FSH) rack; addition of 100µl of the conjugated enzyme to the wells previously containing 25 µl of the positive control, 25 µl of the patient's serum and 25 µl of the standards (6); the system is covered and incubated for 60 minutes at 18˚C - 26˚C; removal of liquid from all wells, followed by three washes with 1X buffer; addition of 100 µl of the TMB substrate to all the wells and incubation for 15 minutes at room temperature followed by addition of 50 µl of the Stop solution to all the wells; reading of the absorbance (ELISA reader at 450 nm) within 15 minutes following the addition of the Stop solution; the concentrations of two (2) different hormones kinds were calculated about the closest optical density (OD) value of the sample among those of the standards.

The testosterone protocol was as follows: preparation of 1X washing buffer as for LH and FSH; placement of the wells in the rack; addition of 100 µl of the conjugated enzyme to all wells containing 50µl of standards, control and patient serum; addition of 50 µl of Biotin to each well and stirring for 20 to 30 seconds; covered plate and incubation for 60 minutes at room temperature; removal of liquid from all wells, followed by 3 washes with 1X buffer (300 µl); dabbing on absorbent paper and adding 100 µl of TMB Substrate to all wells; incubation for 30 minutes at room temperature and addition of 50µl of the Stop solution to all wells; mix the solutions by gently shaking the plate for 15 to 20 seconds; reading of the absorbance on the ELISA reader at 450 nm within 15 minutes following the addition of the Stop solution. calculation of concentrations as with LH and FSH.

2.2.3. Statistical Analyzes

Data extraction and storage was carried out using Microsoft Excel 2016 software. Data were processed and calculations of frequencies and averages used the R software version i386 3.6.3.

3. Results

Hormonal Assessment

The hormonal assessment was abnormal in 48.83% of cases (168/344). Disturbances were observed in the three hormonal parameters (**Table 1**, **Table 2**).

Table 1. Hormonal percentage in infertile men.

Hormones	High rate (%)	Low rate (%)	Normal rate (%)
Testosterone	21 (6.10%)	42 (12.20%)	281 (81.68%)
FSH	49 (14.24%)	28 (8.13%)	267 (77.61%)
LH	7 (2.03%)	21 (6.10%)	316 (91.86%)

Table 2. Distribution of average hormone levels in infertile men.

Hormones	Average and standard deviation		Reference values
	Low	High	
Testosterone (ng/ml)	2.42 ± 0.93	6.94 ± 3.66	3 - 10 ng/ml [Kadima]
FSH (UI/L)	1.32 ± 6.08	17.05 ± 6.08	1 - 6 UI/L [Kadima]
LH (UI/L)	1.33 ± 2.10	16 ± 2.10	0.8 - 6 UI/L [Kadima]

- Testosterone: low in 12.20% (42/344) and high in 6.10% (21/344) of cases (Table 1).
- FSH: high rate in 14.24% (49/344) of cases and decreased in 8.13% (28/344) of subjects.
- LH: decreased in 6.10% (21/344) and elevated in 2.03% of individuals (7/344).

4. Discussion

The average age of the patients was 39 years with extremes ranging from 17 to 73 years, is close to those in the literature: 44 years [25 to 64 years] in Niger [15].

4.1. Hormonal Disturbance

Usually, the hormonal assessment in infertile men includes the assay of: testosterone, FSH, LH, estrogens, prolactin, inhibin B and anti-Müllerian hormone [16]-[21]. Prolactin and the last two hormones (Sertoli cell markers) were not measured in the present study. The gonadotropins LH, FSH and testosterone have important role in the initiation and maintenance of spermatogenesis. Therefore, defects in the synthesis of these hormones cause male infertility [5].

The hormonal assessment carried out in 344 infertile men showed a disruption of these reproductive hormones in 48.83% (168/344) of cases. Our results in accordance with the literature data show that there is always a variably disrupted hormonal balance in cases of male infertility [15]. The hormonal disturbances make it possible to define the states of hypergonadotropic hypogonadism (high LH, FSH and low testosterone) or hypogonadotropic hypogonadism (low or normal LH, FSH and low testosterone) [10] [15].

4.2. Testosterone

It is a steroid hormone (main androgen) secreted in two organs: mainly (95%) in the testes (by Leydig cells) and the adrenals [22]. It is present in both sexes but at very low levels in women [22] [23]. Therefore, testosterone is considered as the male hormone which is involved in the formation of gonads, the development of genital organs, normal spermatogenesis and sexuality [20]. Its secretion is under the control of the hypothalamic-pituitary-gonadal axis, precisely: GnRH hormones (gonadotropic releasing hormone) produced by the hypothalamus and LH, FSH produced by the pituitary gland [5] [24].

Testosterone deficiencies are at the origin of pathozoospermia (including oligozoospermia, azoospermia), causes of male infertility (**Table 1**) [21] [25]. Note that physiologically, testosterone levels decrease by 30% from the age of 60 years [26].

In our study, the testosterone values found were especially low (with an average of 2.42 ± 0.93 ng/ml) in 12.20% (42/344) of the cases. These values reflect a state of hypogonadism which is either hypogonadotropic or hypergonadotropic. Note that low testosterone values are also reported in several studies [15].

Concerning sperm results, we mainly found: asthenozoospermia, oligoasthenozoopsermia and azoospermia, as reported in the literature [25] [27] [28] [29]. It should be noted that high testosterone values were observed in 6.10% (21/344) of our cohort.

4.3. FSH

It is a gonadotropin hormone having an alpha subunit (the same as LH) and a specific beta subunit [30]. It controls spermatogenesis by acting on Sertoli cells [5].

Elevated FSH values are the most observed in our study, with an average of 17.05 ± 6.08 in 14.24% (49/344) of individuals in the cohort, thus signing a hypergonadotropic hypogonadism state (**Table 1**). Note that our values are significantly lower than those reported in the literature, which vary from 32.8 to 41.7% [15] [31].

High FSH levels indicate a malfunction of the pituitary gland or testes. It should be noted that the increase in FSH is accompanied by a deficiency in inhibin B, a hormone produced by Sertoli cells which normally inhibits the secretion of FSH and represents a positive biomarker of spermatogenesis in the seminiferous tubules [12] [32]. The state of hypergonadotropic hypogonadism also reported by other authors is observed for example in cases of chronic urogenital infection [10] [15] [33] [34].

However, low FSH values with an average of 1.32 ± 6.08 indicating hypogonadotropic hypogonadism (low testosterone, LH, and FSH) were found in the present study in 8.13% (28/344) of individuals. These low rates are also reported by several other authors [15] [31]. They highlight a lack of stimulation of spermatogenesis by the pituitary FSH and LH, accompanied by sperm abnormalities (azoospermia or oligozoospermia) [35]. The latter state is for example observed in cases of infections, hemochromatosis, tumours, trauma or radiotherapy of the pituitary region [35].

Table 3. Comparison of hormones level with those of diverse countries.

Countries	Testosterone (%)		FSH (%)		LH (%)		References
	Low	High	Low	High	Low	High	
RDC	5.4	94.6	30.1	69.9	83.9	16.1	[34]
Niger	18.7	1.50	36	-	31.25	1.6	[15]
Niger	17.24	82.76	35.42	64.58	-	-	[10]
Nigeria	30.1	9.4	0.6	5.3	1.57	4.4	[36]
Congo	11.91	6.10	8.13	14.24	6.10	2.03	Present study

DRC: Democratic Republic of Congo.

4.4. LH

It is produced by the pituitary gland and has a positive action on Leydig cells in which it stimulates the secretion of testosterone [23].

In the present work, LH mainly presents low values (**Table 1**) with an average of 1.33 ± 2.10 IU/l in 6.10% (21/344) of the subjects studied.

High values of LH were weakly observed with an average of 16 ± 2.10 IU/l in 2.03% (7/344) of cases. It should be noted that in the majority of cases, 91.86% (316/344), normal LH values were found.

Our data are not in discordance with those in the literature. Indeed, low LH levels associated with high FSH values have been reported in some studies (**Table 3**) [15] [34]. However, high levels of LH are also reported [36] [37].

We can note that: on the one hand, LH deficiencies point to a primary abnormality of the hypothalamic-pituitary axis with secondary testicular impact. This condition happens for example in the case of KISS1R mutations [13] [38]. On the other hand, high LH values point towards a primary testicular abnormality. Examples: Klinefelter syndrome (which is a state of hypergonadotropic hypogonadism), testicular traumatisms, tumours and chronic infections [21]. It can also involve abnormalities in androgen or estrogen receptor genes [4] [39].

5. Limitations

No assay of prolactin, inhibin, estrogens and antimullerian hormone, was performed in this study.

6. Conclusions

The results of hormonal assays (LH, FSH, and testosterone) show that male infertility concerns both the hypothalamus-pituitary axis and the testes. The most observed pattern is hypogonadism with high FSH and low LH.

Establishing the hormonal profile in cases of infertility is, therefore, crucial because it is of great interest in etiological research and the implementation of treatment.

Declarations

Competing Interest

The authors declare no conflict of interest.

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Authors' Contributions

PH designed the study; MC performed the hormone assays; MC, DDRC, OAWS, NNU, PGE and ME contributed to the case collection. PH and MC analyzed the data and wrote the paper.

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