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Original Research Article

Relation between serum hormones and semen parameters in sub-fertile males: is 17-hydroxyprogesterone really a game changer?

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ABSTRACT

Background: Semen analysis and serum hormone assessment remains an integral part of assessment of infertile males. 17-OHP has recently been demonstrated as a very good marker of intratesticular testosterone environment. Our study was designed to find relationship between individual serum hormone levels and semen parameters in sub fertile men, and to find whether 17-OHP fares better or worse in predicting baseline semen parameters compared to other routinely tested hormones.
Methods: A retrospective analytical study was conducted on 74 patients, after matching inclusion and exclusion criteria, from July 2022 to December 2023. All included patients were investigated with Semen analysis and Serum biomarker levels (FSH, total testosterone, estradiol, total testosterone/estradiol (T/E2) ratio, and 17-hydroxyprogesterone).
Results: Only 10 patients (13.51%) had normal semen analysis, while rest 64 (86.49%) had abnormality in at least 1 semen parameter. Serum testosterone and T/E2 ratio had significant difference ($p<0.05$) between the two groups. Comparing individual semen parameters against all hormones, FSH and total testosterone had significant association with sperm count, concentration and total motility. Total testosterone also had a significant relation with progressive motility, morphology and semen volume ($p<0.05$). T/E2 ratio had significant association with Sperm count, motility and morphology, and semen volume ($p<0.05$). But, 17-OHP and estradiol were not found to have any significant association with any baseline semen parameters in our study ($p>0.05$). But, serum 17OHP was found to be significantly associated with sexual dysfunction in males ($p<0.05$).
Conclusions: Our study inferred that serum FSH, testosterone level and T/E2 ratio can be used to predict baseline semen parameters, but 17OHP did not have any association with baseline semen parameters. However, serum 17OHP can serve as a novel marker for male sexual dysfunction.

Keywords: Male infertility, Semen analysis, 17-OHP, Testosterone, FSH, Estradiol, Sexual dysfunction

INTRODUCTION

Infertility has become a serious health problem worldwide. Nearly 10-15% of couples at optimal reproductive age suffer from infertility.[1] The present estimation is that up to 7% of men are affected by infertility and 50% of fertility problems of the couple are due to the male factor.[2] Semen analysis remains an integral part of assessment of infertile couples, along with blood tests to determine circulating levels of various hormones in males. Sex hormones (like FSH, estradiol, testosterone) have been demonstrated to play important roles in spermatogenesis and sperm

maturation. FSH Initiates spermatogenesis.[3] LH Stimulates Leydig cells to secrete testosterone, which plays a more critical role in Spermatogenesis in males by direct activation of the androgen receptor in the testes.[3] Estradiol in men is important for modulating libido, erectile function, and spermatogenesis.[4] A low testosterone to estradiol ratio in males may be associated with poor quality of spermatogenesis.

While serum testosterone does provide some insight into the body's hormonal status, it overall is not a very good reflection of the actual intratesticular testosterone (ITT) levels. Intra-testicular testosterone is of the order of 50-200 times than that of serum testosterone. Spermatogenesis is severely compromised when ITT levels decline. Traditional methods of measuring ITT, however, are invasive testicular biopsy or aspiration. 17-hydroxyprogesterone (17-OHP) is an intermediate in the production of testosterone from cholesterol and it has recently been demonstrated as a reliable bio-marker of intra-testicular testosterone.[5] There is apparent inconsistency in results among various studies comparing serum hormone levels and semen parameters.[6] The relationship between serum hormone levels and semen parameters may provide easier insights into semen quality and status of testicular function. Our study was designed to find a relationship between individual serum hormone levels and baseline semen parameters in sub fertile men and to find whether 17-OHP fares better or worse in predicting baseline semen parameters compared to other routinely tested hormones.

Objectives

Objectives of current study were; to determine an association between different serum biomarkers (17-Hydroxy-progesterone, FSH, total testosterone, estradiol and testosterone/estradiol ratio) and baseline semen parameters in males presenting with subfertility.

METHODS

A retrospective analytical study was conducted at the Institute of Reproductive Medicine and Women's Health (IRM), Madras medical mission hospital, Chennai over a period of 18 months from July 2022 to December 2023.

Inclusion and exclusion criteria

Inclusion criteria were all male patients attending our OPD for treatment of subfertility during the aforementioned time period. Exclusion criteria were men with other endocrinopathies (hypothyroidism, hyper-prolactinemia, Cushing's disease, congenital adrenal hyperplasia, DM) and men already on any medical treatment for male infertility. Total 74 patients were selected in our study by systematic random sampling (Out of total 370 patients in 18 months after meeting inclusion and exclusion criteria, every fifth patient was selected via Systematic random sampling to eliminate bias).

All included patients were investigated with Semen analysis and serum biomarker levels; FSH, total testosterone, estradiol, total testosterone/estradiol (T/E2) ratio, and 17-hydroxyprogesterone. Semen samples were collected after 2-7 days of sexual abstinence and examined following 30 min of liquefaction at 37°C by the same andrologist in the same laboratory according to WHO Semen Analysis manual sixth edition. Serum biomarkers were evaluated from blood samples drawn at the same laboratory between 8 am to 10 am. WHO semen analysis manual 6th edition has defined "normal" semen parameters as above fifth percentile values for fertile men.[7] We have used this as a reference to define normal and abnormal for every parameter in our study. Data was collected and analysed using SPSS version 29, and statistical analyses were done using t test and Chi-squared test.

RESULTS

In our study, total 74 patients were included. The age of study population was between 27-55 years, with mean of 35.68 (±5.94) years and BMI of study population was between 18.7-42.5 kg/m^2, with mean of 28.96 (±3.99) kg/m^2. "Normal" semen analysis is defined as having values of all parameters above fifth percentile values. Out of total 74 patients, only 10 (13.51%) had normal semen analysis, whereas, 64 (86.49%) had abnormality in at least one semen parameter. Hormonal parameters; 17-OHP, FSH, total testosterone, estradiol and total testosterone/ estradiol ratio were compared between these two groups. Mean and SD in normal and abnormal semen analysis groups of these parameters are depicted in (Table 1).

Table 1: Hormone parameters between normal and abnormal semen analysis groups.

Hormones	Normal semen analysis (N=10)	Abnormal semen analysis (N=64)	P value
17-OHP (ng/ml)	0.822±0.206	0.861±0.358	0.369
FSH (mIU/ml)	5.598±1.985	6.238±4.474	0.226
T (nmol/l)	13.018±6.214	9.820±5.015	0.004
E2 (pg/ml)	41.090±16.301	38.270±18.697	0.313
T/E2	9.284±2.372	8.805±5.393	0.030

Only testosterone and T/E2 ratio had significant association with normal semen analysis ($p<0.05$). Then we divided our study population into normal and abnormal based on each semen parameter. Hormonal parameters were compared and analysed between all of these groups (Table 2). Study population was divided into two groups based on sperm count (normal ≥39 million/ejaculate) normal count group 32 (43.24%) and low count group 42 (56.76%). Study population was divided into two groups based on semen volume (normal ≥1.4 ml) normal volume group 59 (79.73%) and low volume group 15 (20.27%).

Study population was divided into two groups based on sperm concentration (normal ≥16 M/ml) normal concentration group 30 (40.54%) and low concentration group 44 (59.46%). Study population was divided into two groups based on total sperm motility (normal ≥42%) normal total motility group 38 (51.35%) and low total motility group 36 (48.65%).

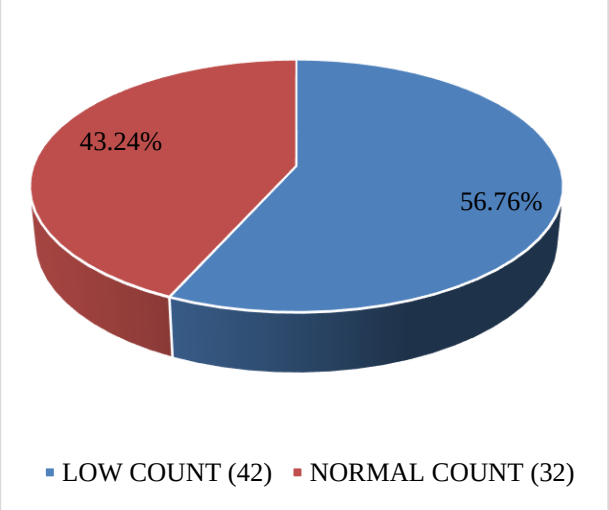

Figure 1: Sperm count distribution in study population.

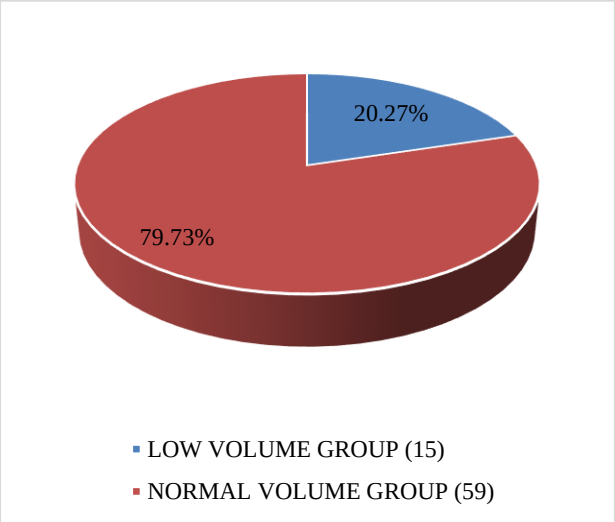

Figure 2: Volume distribution among study population.

Study population was divided into two groups based on progressive sperm motility (normal ≥30%) normal progressive motility 37 (50%) and low progressive motility 37 (50%). Study population was divided based on sperm morphology parameter (normal ≥4%) normal sperm morphology 14 (18.92%) and abnormal sperm morphology 60 (81.08%). Study population was divided based on semen pH parameter (normal ≥7.2) normal pH group 49 (66.22%) and abnormal pH group 25 (33.78%).

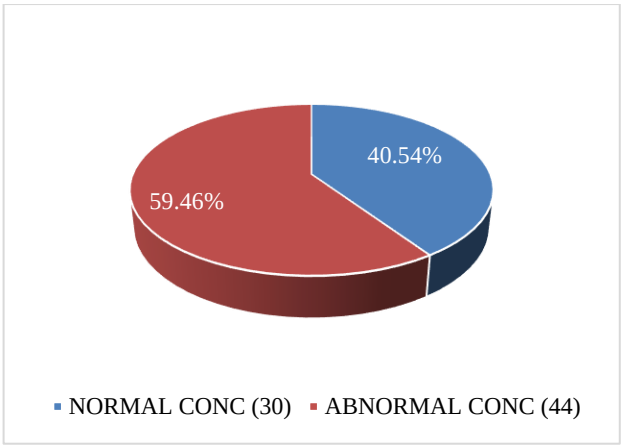

Figure 3: Sperm concentration distribution among study population.

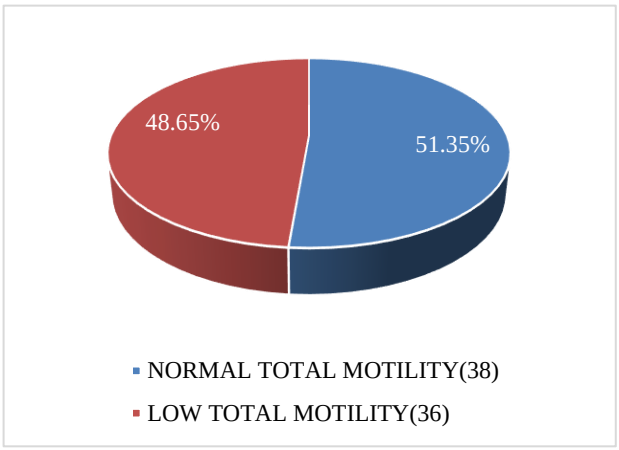

Figure 4: Total motility distribution among study population.

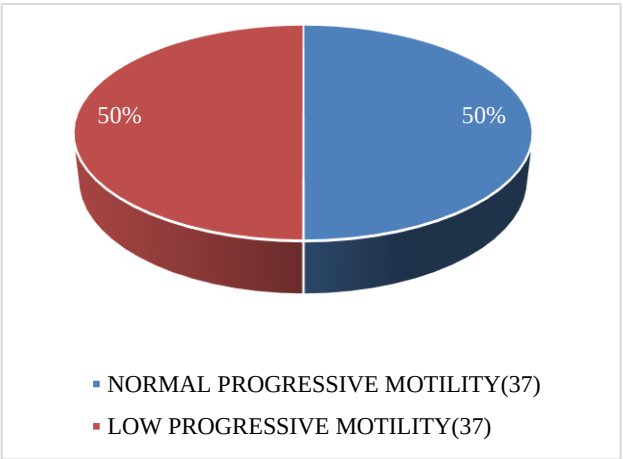

Figure 5: Progressive motility distribution among study population.

As seen in (Table 2), serum FSH showed significant association with sperm count, sperm concentration and total motility ($p<0.05$).

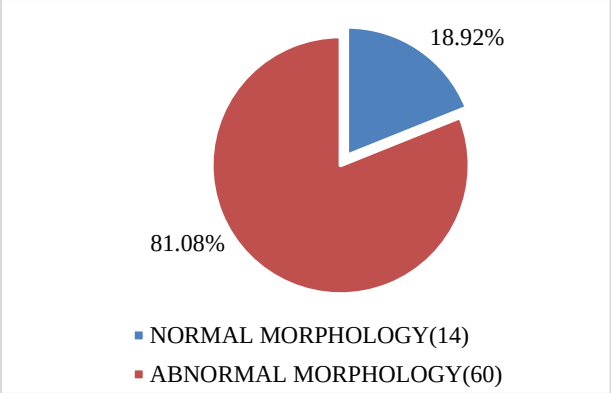

Figure 6: Morphology distribution among study population.

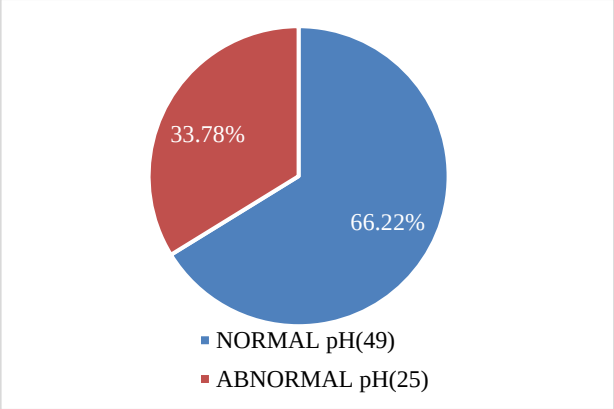

Figure 7: pH distribution among study population.

Table 2: Association of semen parameters with serum hormones in our study population (n=74).

Semen parameters	Hormones	17-OHP (ng/ml)	FSH (mIU/ml)	T (nmol/l)	E2 (pg/ml)	T/E2
Sperm count	Low count	0.873±0.426	7.836±5.562	8.342±5.384	42.719±23.038	7.179±5.771
	Normal count	0.824±0.280	4.869±2.100	12.342±4.835	35.551±13.158	10.792±4.504
	P value	0.285	0.003	0.0008	0.061	0.002
Semen volume	Low volume	0.838±0.371	7.945±6.776	8.067±4.456	42.713±22.877	6.684±4.235
	Normal volume	0.847±0.347	5.696±3.208	11.259±5.490	37.618±17.043	9.877±5.459
	P value	0.466	0.115	0.013	0.215	0.011
Sperm concentration	Low concentration	0.820±0.412	7.568±5.644	8.658±5.688	39.447±21.895	7.966±6.064
	Normal concentration	0.863±0.303	5.186±2.528	11.944±4.864	38.108±15.664	10.091±4.712
	P value	0.316	0.018	0.006	0.387	0.056
Total motility	Low total motility	0.821±0.386	7.083±5.101	9.456±5.667	41.182±20.090	7.968±5.769
	Normal total motility	0.869±0.314	5.270±2.979	11.707±5.014	36.253±16.364	10.425±4.722
	P value	0.280	0.035	0.038	0.126	0.025
Progressive motility	Low progressive motility	0.848±0.399	6.955±5.089	9.335±5.536	40.285±20.274	8.118±5.774
	Normal progressive motility	0.843±0.297	5.349±2.981	11.889±5.066	37.016±16.235	10.341±4.744
	P value	0.475	0.052	0.021	0.223	0.037
Morphology	Abnormal morphology	0.848±0.376	6.282±4.558	9.659±4.989	38.496±18.988	8.718±5.553
	Normal morphology	0.835±0.211	5.592±2.298	14.699±5.487	39.314±15.699	11.421±3.917
	P value	0.433	0.211	0.003	0.434	0.021
Semen pH	Normal pH	0.865±0.333	5.805±3.618	11.454±5.017	38.552±16.268	9.647±4.669
	Abnormal pH	0.807±0.384	6.831±5.221	8.961±5.905	38.844±22.154	8.411±6.551
	P value	0.261	0.192	0.078	0.477	0.202

Serum testosterone was significantly associated with sperm count, semen volume, sperm concentration, total motility, progressive motility and sperm morphology ($p<0.05$). T/E2 ratio was significantly associated with sperm count, semen volume, total motility, progressive motility and sperm morphology ($p<0.05$). Serum 17-OHP and estradiol (E2) were not found to have any statistically significant association with any semen parameters. No serum hormone parameter was found to have significant association ($p>0.05$) with semen pH.

Also, in our study population, 61 patients (82.43%) had normal 17-OHP levels (0.55-2 ng/ml), whereas 13 patients (17.57%) had low 17OHP level (<0.55 ng/ml). A surprising trend was observed on comparing these two groups. Prevalence of sexual dysfunction was found to be much higher in low 17-OHP group 46.15%, compared to

14.75% in normal 17-OHP group. This difference of prevalence of sexual dysfunction was found to be statistically significant (p=0.011).

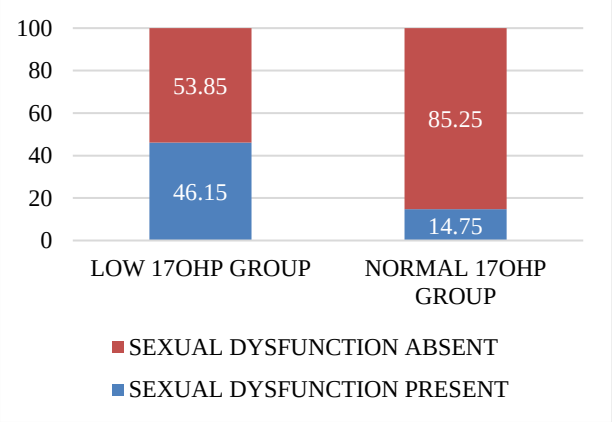

Figure 8: Prevalence of sexual dysfunction between 17-OHP groups.

Table 3: Prevalence of sexual dysfunction between 17-OHP groups.

Sexual dysfunction	Present, N (%)	Absent, N (%)	P value
Low 17-OHP group (N=13)	6 (46.15)	7 (53.85)	0.011
Normal 17-OHP group (N=61)	9 (14.75)	52 (85.25)	

DISCUSSION

We found in our study that FSH and Total Testosterone had significant association with Sperm Count, Concentration and total motility. Total Testosterone also had a significant relation with Progressive Motility, Morphology and Semen volume (p<0.05). Higher serum FSH level is a reflection of lower serum testosterone level due to negative feedback on hypothalamus and pituitary, causing significant effect on spermatogenesis. Testosterone is very important for late stages of spermatogenesis, lower serum testosterone might affect sperm maturation which can result in abnormal sperm concentration, motility and morphology. T/E2 ratio also had significant association with sperm count, motility and morphology, and semen volume (p<0.05). Not only absolute level of serum testosterone, but also T/E2 ratio, i.e. relative abundance of testosterone over estradiol, also was found to play significant effect on basic semen parameters.

Serum 17-OHP level was not found to have any significant association with any baseline Semen parameters in our study (p>0.05). But serum 17OHP level was found to have significant association with male sexual dysfunction; prevalence of sexual dysfunction was found to significantly higher in low 17-OHP group (p=0.011). As serum 17OHP level is a marker of intratesticular testosterone, low local testosterone concentration appears to have significant association with sexual dysfunction in males.

Wei et al found that serum testosterone level correlated well with percent normal sperm count (p=0.031).[8] Prolactin positively correlated with sperm concentration (p=0.019) and total motility (p<0.001). They concluded that these hormone parameters can be used as predictive markers for better semen quality, especially in males with oligoasthenoteratozoospermia syndrome. Our study also found serum testosterone level to be positively and significantly associated with sperm count, concentration, semen volume, total motility, progressive motility and morphology (p<0.05). Uhler et al concluded that serum FSH level has statistically significant association with semen volume, sperm count, concentration and total motility.[9] But there was no significant relationship between the measured hormones and time to pregnancy. This study suggested possible utility of reproductive hormone measurements for predicting semen quality in couples without known reduced fertility. Our study also found serum FSH to be significantly associated with sperm count, concentration and total motility. Meeker et al inferred that FSH was inversely associated and inhibin-B was positively associated with sperm concentration, motility, and morphology.[10] And there was positive association between testosterone and sperm motility. Our study also found FSH and testosterone to be associated with sperm count, concentration and motility. Zhao et al found that serum LH, FSH and Total testosterone were significantly associated with sperm motility and morphology.[6] We also found similar associations with FSH and Testosterone.

Palani et al concluded that serum TSH, FSH, LH and PRL show a negative correlation but testosterone level shows a positive correlation with semen parameters.[11] Osadchuk et al found significant association of serum LH, FSH and inhibin-B levels with sperm concentration and progressive sperm motility.[12] Our study found serum FSH level to be associated with sperm count, concentration and total motility, but not with progressive motility. Keskin et al found that serum FSH and LH were significantly associated with sperm concentration, total motility, progressive motility and morphology; whereas serum Testosterone level was associated with total motility, progressive motility and morphology.[13]

Our study found serum FSH to be associated significantly with sperm count, concentration and total motility only; not with progressive motility or morphology. And our study also found serum Testosterone level to be associated with sperm count, concentration and semen volume, in addition to motility and morphology. Hofny et al found in that oligozoospermic males with obesity had significantly higher levels of FSH, LH, E2 and Leptin.[14] Our study also found serum FSH to be significantly associated with sperm count, and FSH level was relatively higher in low count group. In our study, although serum E2 level was relatively higher in low count group, that difference was not found to be statistically significant.

Lima et al inferred that serum 17-OHP appears to be a reliable serum marker for intratesticular testosterone levels and thus can predict status of spermatogenesis.[5] But in our study serum 17-OHP was not found to be associated with any semen parameters. Pinkas et al concluded that there was no correlation between serum 17OHP level and baseline semen parameters, and they suggested that until conclusive evidence is detected, routine measurement of 17-OHP in the evaluation of male infertility is not recommended.[15] We found similarly in our study that serum 17OHP was not found to be associated with any baseline semen parameters.

Clinical significance

Our study inferred that serum FSH, total testosterone level and T/E2 ratio can be used to predict baseline semen parameters, and serum 17-OHP level can be used to predict sexual dysfunction in males.

Limitations

Limitations of our study were shorter duration and limited number of study subjects. A larger study of longer duration is mandated in this regard.

CONCLUSION

Current study concluded that FSH and total testosterone had a predictive ability on sperm count, concentration and total motility. Also, total testosterone additionally had predictive ability on progressive motility, morphology and semen volume. These serum parameters can be utilised as a prediction or indirect assessment of semen quality in couples presenting with subfertility, and can be an integral part of routine evaluation for male infertility. Serum 17-OHP level was not found to be associated with any baseline semen parameters in this study. But serum 17-OHP level can function as a promising novel marker for male sexual dysfunction.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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