

# Effect of Thyroxine Replacement on Leydig Cell and Sertoli Cell Function in Men with Hypothyroidism

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## Abstract

**Context:** Thyroid hormones play an important role in reproductive and sexual function in both sexes. Comprehensive information on the ill-effects of hypothyroidism on Leydig cell, Sertoli cell and germ cell function is lacking in the existing literature. **Aims:** To investigate the effect of primary hypothyroidism and its treatment on testicular function – Sertoli cell, Leydig cells, seminal fluid and spermatozoa. **Methods and Material:** This study was carried out as a descriptive study with a before-after study design in the endocrine department of a tertiary care hospital in South India. Forty treatment naïve, overtly primary hypothyroid, consenting male patients were included. Hormones assessed were free T3, free T4, thyroid stimulating hormone, follicle stimulating hormone [FSH], luteinizing hormone [LH], prolactin, testosterone, inhibin B[INHB], and insulin like factor 3[INSL3]. Semen analysis was done according to WHO 2010 guidelines in 37 subjects. Sexual function questionnaires like Androgen Deficiency in Aging Male [ADAM], and Arizona Sexual Experience Scale [ASEX] were used. After ensuring euthyroid state for consecutive 6 months with adequate dose of thyroxine sodium, reassessment of all parameters was done. **Results:** At baseline, 72.5 % had a low serum testosterone value (< 230 ng/dl), 67.56 % had low total sperm motility, 72.97% had low total progressive sperm motility, 80% had low ADAM score and 72.72% had low ASEX score. A raised prolactin level was seen in 32.5% of study subjects. Hypogonadotropic hypogonadism was more common than hypergonadotropic hypogonadism (89.66% vs. 10.34%). On restoration of euthyroidism, all these parameters improved. Serum INSL3 and LH increased significantly after thyroxine replacement, unlike FSH and INHB. **Conclusions:** Leydig cell function seemed more severely affected by hypothyroidism as compared to Sertoli cell function. Among sperm function parameters, motility was predominantly affected.

**Keywords:** Androgen deficiency in aging male, arizona sexual experience scale, hypothyroidism, inhibin B, insulin-like factor 3, semen analysis, sperm motility

## INTRODUCTION

The prevalence of overt hypothyroidism ranges from 4.6% to 10.95%.<sup>[1-3]</sup> Hypothyroidism is less common in males. Thyroid hormones play a significant role in the proliferation, differentiation, and function of the Sertoli cells and Leydig cells. Evaluating gonadal function in hypothyroid patients is often tricky as the usual symptoms of hypogonadism like lethargy, decreased muscle strength, loss of body hair, depressed mood, and libido are common in primary hypothyroidism *per se*. Laboratory assessment of hypogonadism and sexual dysfunction involves the measurement of serum gonadotropins, serum testosterone, and semen analysis. However, there are problems with estimation of serum testosterone-like huge intraindividual day-to-day variability, diurnal variation (values tend to decrease during the noon and evening period),

the accuracy and reliability of the free testosterone assays, and poor correlation with intratesticular testosterone.<sup>[4]</sup> Inhibin B (INHB) and insulin-like factor 3 (INSL3) are hormones secreted from the Sertoli cells and Leydig cells, respectively. Compared to testosterone, they are more specific and less subject to variations. Adequate spermatogenesis depends on the intratesticular testosterone and INSL3 is believed to correlate

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better with intratesticular testosterone.<sup>[5,6]</sup> Semen analysis, though an important tool in the evaluation of male reproductive dysfunction, is often an imperfect tool because there are a lot of intra- and inter-individual variabilities.<sup>[7]</sup> A lot of factors affect the result of a semen analysis—site of collection (laboratory vs home), a period of abstinence, efficiency of the laboratory personnel, etc.<sup>[8]</sup> Controversy exists till now what constitutes a normal sperm parameter. Data on the effect of treatment of male hypothyroidism on reproductive and sexual function are scarce.

## SUBJECTS AND METHODS

Forty treatment-naïve patients diagnosed to have primary hypothyroidism, attending the endocrinology and metabolism outpatient department of a tertiary care hospital in India were recruited for this study. Written informed consent was obtained from all. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institute ethics committee. The exclusion criteria were drug-induced hypothyroidism, subclinical hypothyroidism, patients who were smokers, alcoholics, who had undergone orchiectomy, past history of mumps/trauma/radiation, patients on cancer chemotherapy and other drugs which causing infertility/gonadal dysfunction, patients with pituitary surgery/radiation, and diabetic and hypertensive patients. History and detailed clinical examinations were performed for all participants.

At baseline, fasting venous blood samples were drawn for estimation of the free T4 (fT4), free T3 (fT3), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, total testosterone, INHB, and INSL3. All the patients were requested to answer two sexual function questionnaires namely, androgen deficiency in aging male (ADAM) and Arizona sexual experience scale (ASEX). They were self-administered questionnaires in the native language (Tamil) and the patients were given adequate time (30–60 min) and privacy to fill the questionnaires on their own.

Semen analysis was done after a period of abstinence for at least 3 days. The semen sample was collected by masturbation and was analyzed within an hour of collection. The semen collection, analysis, and reporting were done based on the latest WHO recommendations.<sup>[9]</sup> The following semen parameters were defined as “abnormal”: semen volume <1.5 mL, sperm count <15 × 10<sup>6</sup> per mL or <39 × 10<sup>6</sup> per ejaculate, total motile sperm <40%, and total progressive motile sperm <32%. After this baseline evaluation, all patients were treated with levothyroxine and the dosage was titrated according to TSH levels. Monitoring of TSH was done every 6–8 weeks and all the above mentioned parameters were reassessed after ensuring euthyroidism for a minimum period of 6 months.

### Hormonal assessment

Serum INHB was estimated by enzyme-linked immunosorbent assay (ELISA) technique using the CUSABIO reagent kit. The detection range of this assay was 4–800 pg/mL. Both intra-assay and inter-assay coefficient of variation (CV) was <15%. Serum

INSL3 was estimated by the MyBioSource ELISA kit. The analytical sensitivity of the assay was 1.0 pg/mL with an intra-assay and inter-assay CV of <10% for both. TSH, FT4, FT3, PRL, FSH, LH, and total testosterone were measured by the direct chemiluminescence technique (ADVIA Centaur XP equipment). TSH assay measures TSH concentrations up to 150 μIU/mL (mIU/L) with an analytical sensitivity of 0.010 μIU/mL (mIU/L). The intra-assay CV, inter-assay CV, and total CV of TSH were 2.41, 2.05, and 3.17%, respectively. FT4 assay measures FT4 concentrations up to 12.0 ng/dL with an analytical sensitivity of 0.1 ng/dL. The intra-assay, inter-assay, and total CV of FT4 were 2.54, 2.33, and 3.44%, respectively. FT3 assay measures FT3 concentrations up to 20 pg/mL, with analytical sensitivity of 0.2 pg/mL. The intra-assay, inter-assay, and total CV of FT3 were 2.35, 2.47, and 2.76%, respectively. FSH assay measures FSH concentrations up to 200 mIU/mL (IU/L) with an analytical sensitivity of 0.3 mIU/mL (IU/L). The intra-assay, inter-assay and total CV of FSH were 2.9, 2.7, and 3.9%, respectively. LH assay measures LH concentrations up to 200 mIU/mL (IU/L) with an analytical sensitivity of 0.07 mIU/mL. The intra-assay, inter-assay and total CV of LH were 2.6, 2.3, and 3.5%, respectively. PRL assay measures PRL concentrations up to 200 ng/mL (4240 μIU/mL) with an analytical sensitivity of 0.3 ng/mL (6.4 μIU/mL). The intra-assay, inter-assay and total CV of PRL were 2.3%, 2.0%, and 3.1% respectively. Total testosterone assay measures testosterone concentrations up to 1500 ng/dL with an analytical sensitivity of 10 ng/dL. The intra-assay, inter-assay, and total CV of total testosterone were 2.6, 4.3, and 5.0%, respectively.

Hypogonadism was defined as morning 8 am total testosterone of <230 ng/dL irrespective of the symptoms.<sup>[10]</sup> All low testosterone results were confirmed twice by retesting. Hypogonadotropic hypogonadism was diagnosed when low total testosterone was associated with low/normal LH (LH ≤9.3 mIU/mL).<sup>[11]</sup> Similarly, hypergonadotropic hypogonadism was diagnosed when low total testosterone was associated with elevated LH (LH >9.3 mIU/mL).<sup>[11]</sup>

### Questionnaires

ASEX -This scale has five questions. Each question can have six responses with a minimum score of 1 and a maximum of 6. It analyses the five domains of sexual dysfunction namely the drive arousal, penile erection, vaginal lubrication, ability to reach orgasm, and satisfaction from orgasm. A total ASEX score of 19 or more or a score on any one item of 5 or more or scores on any three individual items of 4 or more represents significant sexual dysfunction. ADAM -This contains 10 questions of “yes” or “no” type. If the answer to question number 1 or 7 is yes or the answer to any other 3 questions is yes, the result is positive implying a high risk of androgen deficiency.

### Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (q25–q75), depending on the distribution

of the variable. Categorical variables are expressed as a percentage. The normality of data was assessed by the Kolmogorov–Smirnov test. Parametric tests like paired t-test and nonparametric tests like Wilcoxon signed-rank test were used to assess whether the observed difference in various parameters before and after treatment of hypothyroidism was significant or not. McNemar’s test was used to test the shift in the frequency after treatment from baseline. A *P* value of <0.05 was taken as significant. All statistical analysis was performed using Statistical Package for Social Sciences version 19.0 (SPSS).

## RESULTS

The flow of patients along the study timeline is summarised in figure 1.

### Semen analysis

The changes in semen analysis and hormones at baseline and follow-up in the study are summarized in Table 1. Only 37 out

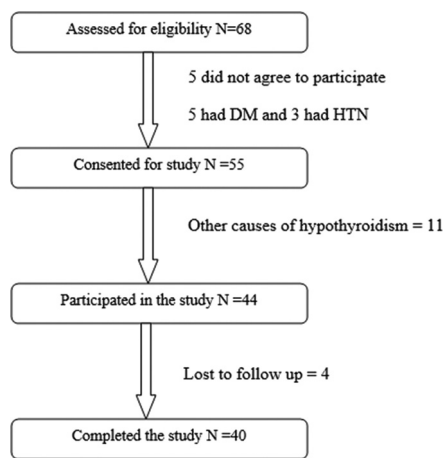


Figure 1: The patient flowchart

of 40 patients gave consent for semen analysis. Low semen volume at baseline was seen in only two patients (5.4%). Both these patients’ semen volume normalized after treatment. The semen pH was normal in all patients at baseline, that is, >7.2. A statistically significant change after treatment was noted in parameters like median semen volume and sperm count. Semen pH and sperm morphology did not change significantly. Sperm concentrations of <math>15 \times 10^6</math> per mL of semen and less than <math>39 \times 10^6</math> per ejaculate were seen in three (8.1%) and five (13.5%) patients, respectively. The proportion of patients who had low total motile sperm was 67.56% (25 out of 37 patients) while that with low total progressive sperm motility was 72.97% (27 out of 37 patients). After treatment, all patients with abnormal sperm motility showed significant improvement except one with azoospermia.

### Hormonal parameters

#### Gonadotropins

At baseline, 12.5% (5/40) had high FSH values (>18.1 mIU/mL) which persisted in 7.5% (3/40) even after achieving euthyroidism. Among the 29 patients with low testosterone, four had low LH, three had high LH, and the rest had normal levels. So, hypogonadotropic hypogonadism was seen in 26/29 (89.65%) subjects. After achieving euthyroidism, LH normalized in all four with low levels. Two of the three patients with high LH levels had persistent elevation after treatment. One patient who had normal LH value before treatment had elevated LH after treatment.

#### Testosterone and prolactin

In our study, 72.5% (29/40) had hypogonadism at baseline. After euthyroidism, testosterone levels normalized in all of them except one. Hyperprolactinemia (serum prolactin >17.7 ng/mL) was seen in 32.5% (13/40) patients of which, prolactin levels normalized in 10.

#### INSL3 and INHB

Serum INSL3 showed a statistically significant rise after achieving euthyroidism. Concomitantly, a nonsignificant

Table 1: Changes in semen analysis and hormones at baseline and follow-up

Parameter	Baseline Median q25-q75	Follow-up Median q25-q75	<i>P</i>
Semen analysis (37 out of 40 patients)			
Total motile sperm %	30 (16.25-48.75)	80 (68.50-90)	<0.01*
Total progressive motile sperm %	19 (10-38.70)	48 (42-60.20)	<0.01*
Total non-progressive motile sperm %	5 (4.50-10)	27 (18-35)	<0.01*
Sperm count/ejaculate (million)	165 (120-236.20)	250 (160-342.50)	<0.01*
Hormones (40 patients)			
Serum FSH (mIU/mL)	6.48 (4.10-9.11)	6.48 (4.43-9.96)	0.48
Serum LH (mIU/mL)	3.49 (2.31-5.96)	4.36 (3.40-7.10)	0.03*
Serum prolactin (ng/mL)	10.875 (8.21-19.20)	8.10 (5.37-13.59)	<0.01*
Serum testosterone (ng/dL)	161.535 (114.84-232.22)	441.43 (357.13-491.60)	<0.01*
Serum INSL3 (pg/mL)	1.000 (1.00-1.58)	50.64 (16.62-111.52)	<0.01*
Serum inhibin B (pg/mL)	298.25 (137.97-429.27)	284.16 (173.37-434.80)	0.24
Serum TSH (mIU/mL)	172.35 (107.47-344.71)	2.37 (1.31-3.48)	<0.01*

TSH: Thyroid stimulating hormone; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; INSL3: Insulin-like factor 3; INHB: Inhibin B.

\*Significant. Normal reference range. TSH: 0.35-5.5 mIU/mL; FSH: 1.4-18.1 mIU/mL; LH: 1.5-9.3 mIU/mL; prolactin: 2.1-17.7 ng/mL; testosterone: 230-827 ng/dL

decrease in serum INHB was noted after levothyroxine treatment.

### Questionnaires

Only 87.5% (35/40) answered the ADAM questionnaire, out of which 80% (28/35) scored positive for androgen deficiency. Similarly, 82.5% (33/40) answered the ASEX questionnaire, out of which 72.72% (24/33) scored positive for sexual dysfunction. After treatment, all patients who had scored positive for androgen deficiency and sexual dysfunction in ADAM and ASEX respectively improved to normalcy scores.

### DISCUSSION

Hypothyroidism, a common endocrine problem is known to cause significant disturbances in male reproductive function. The effect of hypothyroidism and its treatment on individual parameters like semen analysis, gonadotropins, prolactin, testosterone, INHB, and INSL3 has not been well studied till now. Studies in the rat have shown that hypothyroidism causes arrest of spermatogenesis.<sup>[12]</sup> In humans, similar studies done till now are heterogeneous, with regards to the number of patients included, the way semen analysis was reported, and whether the posttreatment effect was analyzed or not. Studies on the effect of hypothyroidism on semen parameters done till now show a negligible effect of hypothyroidism on semen volume, except one by Corrales *et al.*, where a statistically significant difference was found in the mean semen volume between patients and controls ( $2.7 \pm 1.4$  vs.  $3.7 \pm 1.2$ ).<sup>[13-15]</sup> Sperm motility and sperm count, the two important sperm parameters were differentially affected in our study. Sperm motility was the most affected parameter in our study unlike that in the study by Corrales *et al.* where it was normal.<sup>[15]</sup> Sperm count at baseline was not affected significantly similar to the studies by Krassas *et al.* and Nikoobakht *et al.*<sup>[16,17]</sup> Hypothyroidism can affect sperm motility through various mechanisms like increase in the levels of reactive oxygen species (ROS) which alter the sperm cell membrane, changes in the pH of the semen, abnormal activity of  $\text{Na}^+ \text{K}^+$  ATPases, altered transmembranous transport of calcium in the sperm cell membrane, mitochondrial number, expression of mitochondrial genes, and secretions from the prostate and seminal vesicle.<sup>[18-21]</sup>

More than two-thirds (72.5%) of our patients had low testosterone at baseline. Low testosterone in patients with hypothyroidism has been well documented in most of the studies with varying prevalence.<sup>[22-24]</sup> All eight patients (100%) in the study by Jayakumar *et al.* had low testosterone at baseline, while 7 out of 10 patients (70%) studied by Donnelly *et al.* had low testosterone at baseline.<sup>[24,25]</sup> Velazquez *et al.* demonstrated normal free testosterone in all the five hypothyroid patients they studied.<sup>[26]</sup> The possible mechanisms by which hypothyroidism causes low total testosterone include reduced uptake of cholesterol into the steroidogenic cells for testosterone synthesis, inhibition of the enzymes converting progesterone to testosterone, decrease in serum

sex hormone-binding globulin level, hyperprolactinemia, increased rate of conversion of testosterone to estradiol, and decrease in the secretion of gonadotropins. In our subjects, around one-third had high prolactin levels at baseline, which is expected as hypothyroidism is known to cause high prolactin levels as demonstrated by Jayakumar *et al.*, Donnelly *et al.*, and Honbo *et al.*<sup>[24,25,27]</sup> Severe hypothyroidism can rarely cause secondary hyperplasia of the pituitary gland. This might be another rare mechanism of hypogonadotropic hypogonadism in hypothyroidism. Unfortunately, we were not able to imagine the pituitary in our subjects. The type of hypogonadism associated with hypothyroidism could be either hypogonadotropic hypogonadism or hypergonadotropic hypogonadism. Most of the studies published until now reported hypogonadotropic hypogonadism except the one by Jayakumar *et al.* where hypergonadotropic hypogonadism was predominant.<sup>[22-26]</sup> In our subjects, hypogonadotropic hypogonadism was more common than hypergonadotropic hypogonadism.

In a study of 14 hypothyroid male patients by Donnelly *et al.*, the mean INHB level was  $87 \pm 14$  pg/mL while in the normal controls, it was  $158 \pm 9$  pg/mL. However, semen analysis was not done in this study.<sup>[28]</sup> In our subjects, INHB values at baseline were comparable to that of the normal controls of two studies done in the Indian population by Geetika *et al.* and Abid *et al.*<sup>[29,30]</sup> While we did not observe a significant change in INHB values before and after treatment, levels of serum INSL3, a hormone secreted by the Leydig cells, increased significantly after the achievement of euthyroidism. The source of INHB was believed to be exclusively from Sertoli cells, till recently. In a study by Marchetti *et al.*, it was shown that the mRNA of INHB was also expressed in various stages of germ cells.<sup>[31]</sup> Thus, the serum levels of INHB could reflect a joint contribution of germ cells and Sertoli cells.

One interesting observation from this study is that the effect of hypothyroidism on the testicular cells does not seem to be uniform. The presence of a normal sperm count in the majority of our study subjects at baseline, the absence of a significant change in INHB after thyroxine replacement and marked improvement in serum testosterone and INSL3 after thyroxine replacement suggests that Leydig cells could be preferentially affected more than Sertoli cells in male hypothyroidism patients. The reasons are difficult to infer from this study. Probable explanations are differential susceptibility of the cells depending on the duration and severity of hypothyroidism, alteration in the paracrine regulatory factors governing the Sertoli and Leydig cell function, effect of hypothyroidism not only on the Leydig cell structure but also on the steroidogenic enzymatic pathways. To confirm these mechanisms, we need further long term studies.

The main strength of the present study is a comprehensive assessment of functions of all cellular components of the testis in the largest group of primary, treatment-naïve, hypothyroid patients published till now. It is also the first study to analyze

INSL3, a robust marker of intratesticular testosterone concentration in hypothyroid patients. The main limitations of the present study are the lack of a control group, small sample size, absence of neuroimaging and our inability to assess free or bioavailable testosterone.

## CONCLUSION

To conclude, Leydig cell function was more severely affected than Sertoli cell function in overt hypothyroidism. Among semen parameters, sperm motility was predominantly affected. Restoration of euthyroidism led to almost complete normalization of the majority of the deranged parameters. Though it is common knowledge that hypothyroidism affects the function of gonads, this study throws more light, albeit a smaller one, on the consequences of hypothyroidism on the specific individual components of the testis and raises interesting questions.

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## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

- Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, *et al.* Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 2002;87:489-99.
- Sawin CT, Castelli WP, Hershman JM, McNamara P, Bacharach P. The aging thyroid: Thyroid deficiency in the Framingham study. *Arch Intern Med* 1985;145:1386-8.
- Unnikrishnan AG, Menon UV. Thyroid disorders in India: An epidemiological perspective. *Indian J Endocrinol Metab* 2011;15 (Suppl 2): S78-81.
- Brambilla DJ, O'Donnell AB, Matsumoto AM, McKinlay JB. Intraindividual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. *Clin Endocrinol (Oxf)* 2007;67:853-62.
- Coviello AD, Bremner WJ, Matsumoto AM, Herbst KL, Amory JK, Anawalt BD, *et al.* Intratesticular testosterone concentrations comparable with serum levels are not sufficient to maintain normal sperm production in men receiving a hormonal contraceptive regimen. *J Androl* 2004;25:931-8.
- Roth MY, Lin K, Bay K, Amory JK, Anawalt BD, Matsumoto AM, *et al.* Serum insulin-like factor 3 is highly correlated with intratesticular testosterone in normal men with acute, experimental gonadotropin deficiency stimulated with low-dose human chorionic gonadotropin: A randomized, controlled trial. *Fertil Steril* 2013;99:132-9.
- Vasan SS. Semen analysis and sperm function tests: How much to test? *Indian J Urol* 2011;27:41-8.
- Shetty Licht R, Handel L, Sigman M. Site of semen collection and its effect on semen analysis parameters. *Fertil Steril* 2008;89:395-7.
- Trevor G Cooper, WHO laboratory manual for the examination and processing of human semen - 5<sup>th</sup> ed. Geneva, WHO publications, 2010.
- Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, *et al.* Investigation, treatment and monitoring of late-onset hypogonadism in males. *Eur J Endocrinol* 2008;159:507-14.
- Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, *et al.* Testosterone therapy in men with hypogonadism: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2018;103:1715-44.
- Condorelli RA, La Vignera S, Mongioi LM, Alamo A, Giacone F, Cannarella R, *et al.* Thyroid Hormones and Spermatozoa: In Vitro Effects on Sperm Mitochondria, Viability and DNA Integrity. *J Clin Med* 2019;8:756.
- Griboff SI. Semen analysis in myxedema. *Fertil Steril* 1962;13:436-43.
- De La Balze FA, Arrillaga F, Mancini RE, Janches M, Davidson OW, Gurtman AI. Male hypogonadism in hypothyroidism: A study of six cases. *J Clin Endocrinol Metab* 1962;22:212-22.
- Corrales Hernández JJ, Miralles García JM, García Díez LC. Primary hypothyroidism and human spermatogenesis. *Arch Androl* 1990;25:21-7.
- Krassas GE, Papadopoulou F, Tziomalos K, Zeginiadou T, Pontikides N. Hypothyroidism has an adverse effect on human spermatogenesis: A prospective, controlled study. *Thyroid* 2008;18:1255-9.
- Nikoobakht MR, Aloosh M, Nikoobakht N, Mehraiy AR, Biniyaz F, Karjalainen MA. The role of hypothyroidism in male infertility and erectile dysfunction. *Urol J* 2012;9:405-9.
- Zamoner A, Barreto KP, Filho DW, Sell F, Woehl VM, Guma FC, *et al.* Propylthiouracil-induced congenital hypothyroidism upregulates vimentin phosphorylation and depletes antioxidant defenses in immature rat testis. *J Mol Endocrinol* 2008;40:125-35.
- Sati L, Huszar G. Sperm Motility and Viability: Overview of the Cellular and Physiological Aspects That Support These Functions. *EMJ Repro Health* 2015;1:74-80.
- Zhou J, Chen L, Li J, Li H, Hong Z, Xie M, *et al.* The semen pH affects sperm motility and capacitation. *PLoS One* 2015;10:e0132974.
- Koçak-Toker N, Aktan G, Aykaç-Toker G. The role of Na, K-ATPase in human sperm motility. *Int J Androl* 2002;25:180-5.
- Kumar A, Chaturvedi PK, Mohanty BP. Hypoandrogenaemia is associated with subclinical hypothyroidism in men. *Int J Androl* 2007;30:14-20.
- Wortsman J, Rosner W, Dufau ML. Abnormal testicular function in men with primary hypothyroidism. *Am J Med* 1987;82:207-12.
- Jaya Kumar B, Khurana ML, Ammini AC, Karmarkar MG, Ahuja MM. Reproductive endocrine functions in men with primary hypothyroidism: Effect of thyroxine replacement. *Horm Res* 1990;34:215-8.
- Donnelly P, White C. Testicular dysfunction in men with primary hypothyroidism; reversal of hypogonadotrophic hypogonadism with replacement thyroxine. *Clin Endocrinol (Oxf)* 2000;52:197-201.
- Velázquez EM, Bellabarba Arata G. Effects of thyroid status on pituitary gonadotropin and testicular reserve in men. *Arch Androl* 1997;38:85-92.
- Honbo KS, Herle AJV, Kellett KA. Serum prolactin levels in untreated primary hypothyroidism. *Am J Med* 1978;64:782-7.
- Donnelly P, Tan K, Winch D. Inhibin B levels in hypothyroid males. *Thyroid* 2013;23:1379-82.
- Geetika, Gupta S, Sikarwar S. Role Of Serum Hormone Indices Including Inhibin B And Scrotal Ultrasound In Evaluation Of Non Obstructive Male Factor Infertility. *WebmedCentral Reproduction* 2011;2:WMC001510.
- Abid S, Maitra A, Meherji P, Patel Z, Kadam S, Shah J, *et al.* Clinical and laboratory evaluation of idiopathic male infertility in a secondary referral center in India. *J Clin Lab Anal* 2008;22:29-38.
- Marchetti C, Hamdane M, Mitchell V, Mayo K, Devisme L, Rigot JM, *et al.* Immunolocalization of inhibin and activin alpha and beta subunits and expression of corresponding messenger RNAs in the human adult testis. *Biol Reprod* 2003;68:230-5.