UDC 578.834.1+612.663 doi: https://doi.org/10.15407/ubj96.03.031

THE LEVEL OF SEX AND FERTILITY HORMONES IN THE SERUM OF MALE PATIENTS RECOVERED FROM COVID-19

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Received: 20 March 2024; **Revised:** 30 April 2024; **Accepted:** 31 May 2024

The new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that generated the COVID-19 pandemic is a broad-spectrum infection that besides the respiratory tract, can attack multiple organs, including the digestive, circulatory, and urinary systems. However, the negative consequences of SARS-CoV-2 on the male reproductive system have been largely ignored. The aim of this research was to see how SARS-CoV-2 affects the production of hormones, which are the markers of male reproductive function and fertility. The 350 Iraqi male participants were classified into two groups consisting of 150 COVID-19 recovered patients with a mean age of (32 ± 7.9) years and COVID-19 diagnosis confirmed by RT-PCR, and 200 apparently healthy male volunteers of similar age. The patients' group was further divided into three groups depending on the recovery period of 3, 5 and 7 months. Serum levels of testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin were measured using the Mindray CL-1000i automated chemiluminescence analyzer provided with matching kits. When comparing the indices of COVID-19 recovered participants to the control group, the results revealed a decrease in testosterone level that was positively associated with the recovery period and an increase in the LH, FSH and prolactin levels that were negatively associated with the recovery period. It is supposed that infection with SARS-CoV-2 may be followed by a temporary condition of testicular failure.

K e y w o r d s: sex hormones, male fertility, SARS-CoV-2.

Coronavirus disease 2019 is a new global public health disaster that has resulted in significant mortality and morbidity. Beginning in the Chinese city of Wuhan in the Hubei region in December 2019, COVID-19 has since spread to several countries, turning into a pandemic [1]. SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) is a novel beta coronavirus that is the culprit behind COVID-19 [2]. High rates of transmission, phenotypic clinical indications that range from mild to severe, and significant clinical, radiologic, and pathologic issues in elderly people are all characteristics of COVID-19 [3]. Although there is currently investigation into the disease's potential effects on other tissues, the respiratory system is where it is most prevalent. The genus of enclosed viruses known as coronaviruses is large and diverse, and its genetic material is composed of positive-sense single-stranded RNA. The common cold is one of the respiratory conditions caused by these viruses that affect both humans and other species [4]. When seen using transmission electron microscopy, the protein spikes on the envelope of coronaviruses are club-shaped, giving them the appearance of a crown (thus the name) [5]. Other coronavirus members have also been linked to severe respiratory diseases. SARS-CoV (SARS-CoV-1) causes severe acute respiratory syndrome (SARS), and Middle East Respiratory Syndrome-Related Coronavirus (MERS-CoV) [6].

It is believed that ACE2 (angiotensin-converting enzyme 2) is the receptor for SARS-CoV-2 binding and entry into host cells [7, 8].

SARS-CoV-2 might hypothetically infect any cells that contain ACE2. Testes have the highest level of ACE2 protein expression, according to the Human Protein Atlas portal [9]. ACE2 is primarily found in spermatogonia, Leydig, and Sertoli cells, according to Wang ZP et al. [10]. All of the findings point to the male gonad being susceptible to infection with SARS-CoV-2.

Multiple organs, including the digestive, circulatory, and urinary systems, have been attacked by SARS-CoV-2 [11-14]. However, any negative consequences of SARS-CoV-2 on the male reproductive system, particularly the virus's impact on male reproductive hormones, have been largely ignored. Male reproductive hormones have an important role in both male and female sexual development, maturation, and fertility.

Testosterone, the primary sex hormone and anabolic steroid in males, is involved in a variety of physiological functions, including reproductive physiology (e.g., spermatogenesis), morphology (e.g., secondary sexual features improvement), psychology (e.g., sexual inclination), and behavior such as aggression, All of these processes are crucial for survival and reproduction [15].

Luteinizing hormone (LH) is a heterodimeric glycoprotein that has different roles in males and women. Both sexes' primordial germ cells benefit from LH's assistance in maturation. Male Leydig cells in the testes produce testosterone when LH is present. In women, LH causes the ovaries to produce steroid hormones [16].

Follicle-stimulating hormone (FSH) is a glycoprotein that controls the human body's development, growth, pubertal maturation, and reproductive functions. FSH promotes the maturation of primordial germ cells in both males and females. In males, FSH causes Sertoli cells to secrete androgen-binding proteins (ABPs), which is controlled by the anterior pituitary's negative feedback mechanism, inhibin. FSH-stimulated Sertoli cell activation maintains spermatogenesis and induces inhibin B production [17].

Prolactin has several different impacts. It stimulates the mammary glands to produce milk (lactation): increasing serum prolactin level throughout pregnancy causes mammary gland expansion and prepares for milk production, which typically begins when progesterone level declines near the end of pregnancy and a suckling stimulus is present [18]. Prolactin has been linked to male infertility, despite the fact that its functional significance to male reproduction has not been definitively demonstrated. Acute hyperprolactinemia has been shown to limit testosterone synthesis and male fertility by causing adrenal corticoid hypersecretion or blocking GnRH secretion via the receptors of prolactin on hypothalamic dopaminergic neurons [19, 20].

Testicular damage brought on by viruses can reduce spermatogenesis and gonadal hormone release, as seen by HIV and mumps-induced orchitis [21]. Orchitis and SARS-CoV have previously been connected in research [22]. There is yet no clinical proof that a SARS-CoV-2 infection affects the functionality of the male gonads, though. As a result, the goal of this study is to see how SARS-CoV-2 affects the levels of male reproductive hormones (Testosterone, FSH, LH, and prolactin) in a group of Iraqi COVID-19 recovered patients after infection.

Materials and Methods

Study subjects. The 350 male participants in this study were classified into two main categories. The first group consisted of 150 male COVID-19 recovered patients with a mean age of (32 ± 7.9) years whose ages ranged from 28 to 42 years. The other group, which served as the control group, consisted of 200 apparently healthy male volunteers. The control group was (31 8.5) years old on average, with a range of (29–44) years. The patients' group was further divided into three groups depending on the period of recovery from the day of sample collection. The first group (Group A) included 50 subjects with a recovery period of three months. The second group (Group B) included 50 subjects with a recovery period of five months. The third group (Group C), included 50 subjects with a recovery period of seven months from the day of the sample collection. Verbal consent was obtained from the subjects involved in this study. The subjects enrolled in this study were colleagues, acquaintances and random subjects attending private medical labs. The previous diagnosis of the patients with COVID-19 was confirmed by real-time polymerase chain reaction test (RT-PCR). All the study subjects were asymptomatic and negative for active infections with SARS-CoV-2 at the time of sample collection. This study was approved by the Ethics Committee (approval No. 113 at 19/Dec/2021) in the Department of Molecular and Medical Biotechnology, College of Biotechnology, Al-Nahrain University.

Exclusion criteria. In order to prevent any potential impact on the study results, the following subjects were omitted from the study: patients who were infected with SARS-CoV-2 at the time of sample collection, patients suffering from male reproductive diseases, patients under current or previous hormonal therapy, patients with any known inflammatory condition, subjects using steroid supplements and finally, smokers were also excluded.

Collection and storage of blood samples. By puncturing veins with plastic disposable syringes, 5 ml of venous blood samples were obtained from each patient and a healthy control. In order to start the coagulation process, the blood was placed in a gel tube and maintained at room temperature for 15–30 min. The gel tube was then centrifuged at 3500 xg for fifteen minutes to separate the serum. The samples were analyzed immediately after collection.

Measurement of testosterone, FSH, LH and prolactin. Testosterone, FSH, LH and prolactin were measured in the sera of all the study subjects using the chemiluminescence automated analyzer (Mindray CL-1000i, China) provided with kits manufactured by Mindray Medical International Limited. All of the samples were analyzed in triplicate form.

Statistical analyses. Statistical package for social sciences (SPSS) software (version 25) was used to analyze biochemical data. Student's *t*-test, One-Way ANOVA and Pearson Correlation were used in order to assess the results of this study.

Results and Discussion

Because spermatogenesis and androgen secretion are the main functions of the testes, sex-related hormones can also be utilized to assess the condition of the male reproductive organ. To show how the COVID-19 recovery process affected men's ability to reproduce, we compared the sex hormone profiles of recovered COVID-19 patients to those of age-matched, fertile males in the general population. Accordingly, this study involved measuring the serum levels of testosterone, FSH, LH and prolactin in 150 COVID-19 recovered males and 200 apparently healthy controls. The levels of these hormones in the patients and control groups are mentioned in Table 1.

In order to investigate the post-infection severity of the COVID-19 impact on the gonadal function in the males of this study, we divided the subject into three groups depending on the recovery period of the patients as stated earlier. The levels of testosterone, LH, FSH and prolactin measured in subjects after three, five and seven months from full recovery are shown in Table 2.

As it can be seen from the results in Table 2, there is a positive correlation between testosterone serum levels and the recovery period. The serum level of testosterone was significantly lower (2.71 ± 0.53) after three months from full recovery compared to its level after five and seven months from full recovery (3.6 ± 0.27 and 4.72 ± 0.46 respectively). The levels of testosterone increased significantly ($P < 0.0001$) moving from group A to C (Group A: three months recovery, Group B: five months recovery, Group C: seven months recovery). Although the level of testosterone was within the lower limit of the normal range, it seems that as the recovery period from COVID-19 increased, the serum level of testosterone started to increase as well. This observation confirms the effect of Covid-19 on the levels of hormones and the effect of the virus on the hypothalamus-pituitary-gonadal axis in general.

Our findings, on the other hand, revealed that the serum levels of LH, FSH and prolactin were significantly higher after three months from full recovery compared to their levels after five and seven months from full recovery. A significant decline ($P < 0.0001$) in the concentrations of these hormones is observed as the recovery period is increased.

Pearson correlation was determined in order to assess the presence of a statistical correlation between the parameters as shown in Tables 3–6 below.

Judging from the results in Tables 3–6, it is obvious that there is a significantly negative correlation between testosterone and the other hormones. However, there was a significant positive correlation between LH and both FSH and prolactin, while a

Table 1. Serum levels of testosterone, LH, FSH and prolactin in the COVID-19 recovered patients and control groups

Parameters	Groups	
	COVID-19 (mean ± SD, n = 150)	Control (mean ± SD, n = 200)
Testosterone, ng/ml	3.68 ± 0.93	7.29 ± 1.76
LH, mIU/ml	8.00 ± 1.76	4.05 ± 1.17
FSH, mIU/ml	7.29 ± 2.61	4.12 ± 1.04
Prolactin, ng/ml	16.32 ± 2.89	7.67 ± 2.23

Note. $P \leq 0.05$

Table 2. Serum levels of testosterone, LH, FSH and prolactin in the COVID-19 recovered patients based on the recovery period

Parameters	COVID-19 groups, *n* = 50	mean ± SD	*P*-value, (A vs B)	*P*-value, (A vs C)	*P*-value, (B vs C)
Testosterone, ng/ml	Group A	2.71 ± 0.53	1×10^{-4}*	1×10^{-4}*	1×10^{-4}*
	Group B	3. 6 ± 0.27			
	Group C	4.72 ± 0.46			
LH, mIU/ml	Group A	9.76 ± 1.16	1×10^{-4}*	1×10^{-4}*	1×10^{-4}*
	Group B	8.04 ± 0.16			
	Group C	6.19 ± 1.24			
FSH, mIU/ml	Group A	10.00 ± 0.96	1×10^{-5}*	1×10^{-5}*	1×10^{-5}*
	Group B	7.77 ± 0.37			
	Group C	4.10 ± 1.24			
Prolactin, ng/ml	Group A	18.62 ± 1.37	1×10^{-4}*	1×10^{-5}*	1×10^{-5}*
	Group B	17.04 ± 0.26			
	Group C	13.29 ± 2.85			

*Significant at the level ≤ 0.05. SD –standard deviation, *n* – number of subjects. Group A –three months recovery, Group B – five months recovery, Group C – seven months recovery

Table 3. Pearson correlation between testosterone and other parameters

Testosterone vs parameters	Correlation (*r*)	*P*-value
LH	-0.902	1×10^{-6}*
FSH	-0.954	1×10^{-6}*
Prolactin	-0.874	1×10^{-5}*

*Significant at the level ≤ 0.05. *r* – pearson correlation

Table 4. Pearson correlation between LH and other parameters

LH vs parameters	Correlation (*r*)	*P*-value
Testosterone	-0.902	1×10^{-6}*
FSH	0.924	1×10^{-6}*
Prolactin	0.931	1×10^{-6}*

*Significant at the level ≤ 0.05. *r* – pearson correlation

significantly negative correlation was found between LH and testosterone. The same applies to FSH and prolactin. In both FSH and prolactin, there was a significant negative correlation with testosterone, while there was a significant positive correlation with other hormones.

The results of the present study suggest that some of the subjects enrolled may have suffered from testicular failure (also known as primary hypogonadism), reflected by the low-normal serum levels of testosterone and the elevated levels of LH, FSH and prolactin. When elevated FSH and LH levels are combined with low-normal or below-normal testosterone levels, it indicates generalized testicular failure, which could be congenital (e.g., Klinefelter syndrome) or acquired [23-27].

Although the hormone's physiological significance to male reproduction has not been definitively demonstrated, it has been linked primarily to male infertility. As mentioned earlier, our results showed a significantly negative correlation between testosterone and prolactin, showing elevated levels of prolactin with low levels of testosterone in the study subjects. Acute hyperprolactinemia has been shown to limit testosterone synthesis and male fertility by causing adrenal corticoid hypersecretion or blocking GnRH secretion via receptors of prolactin on hypothalamic dopaminergic neurons [28, 29]. Endorphin release from opioidergic neurons is hypothesized to be influenced by dopamine, which limits GnRH production [30].

Male infertility has also been attributed to disturbances in reproductive hormones (testosterone, follicle-stimulating hormone, luteinizing hormone and prolactin). Therefore, these hormones are also assessed in clinical practice for the screening and

Table 5. Pearson correlation between FSH and other parameters

FSH vs parameters	Correlation (*r*)	*P*-value
LH	0.924	1×10^{-6}*
Testosterone	-0.954	1×10^{-6}*
Prolactin	0.918	1×10^{-6}*

*Significant at the level ≤ 0.05. *r* – pearson correlation

Table 6. Pearson correlation between prolactin and other parameters

Prolactin vs parameters	Correlation (*r*)	*P*-value
LH	0.931	1×10^{-6}*
FSH	0.918	1×10^{-6}*
Testosterone	-0.874	1×10^{-5}*

*Significant at the level ≤ 0.05. *r* – pearson correlation

diagnosis of infertility causes. Gonadotropins (FSH, LH), as well as testosterone, are the prime regulators of germ cell development. Abnormal spermatogenesis is frequently linked with altered serum gonadotropins and testosterone. In a study by Ramesh et al., in 96 infertile males, the levels of FSH, LH, and testosterone were evaluated. Of these, 35 had azoospermia, 35 had oligospermia, 11 had varicocele, and 15 had histological abnormalities like hypospermatogenesis, spermatid arrest, and sertoli-cell only syndrome. When compared to the fertile controls ($n = 35$), the results demonstrated a statistically significant ($P \leq 0.05$) rise in the mean FSH and LH levels in all the infertile males tested. Furthermore, there was no discernible difference between the infertile and fertile men in the mean levels of testosterone [31].

So far, only three studies have examined how SARS-CoV-2 affects male reproductive hormones. In the first study, Ma L. et al. revealed the first non-peer-reviewed data associating SARS-CoV-2 infection with male sex hormone abnormalities. The researchers studied sexrelated hormones in 81 reproductive-aged males infected with SARS-CoV-2 and 100 healthy men of similar age. Although blood testosterone levels were not statistically different between the two groups, recovered patients had significantly higher serum LH levels and lower tes-tosterone: LH and follicle stimulating hormone: LH ratios than healthy controls. In the second study, Rastrelli G. et al. [32] found that total testosterone levels were adversely connected to CRP levels in COVID-19 recovered patients, with low total testosterone levels seen in the most severe cases. Males with COVID-19 tended to have low levels of both testosterone and dihydrotestosterone, according to the third study from Germany [33]. These findings imply that hypogonadism might be a risk factor for COVID-19, leading to increased morbidity and mortality. However, none of the earlier studies investigated the levels of the male hormones after recovery from the infection and the correlation between the recovery period and the abnormalities found in the levels of the corresponding hormones. To the best of our knowledge, this study is the first to examine the effect of recovery time on the levels of male and fertility hormones, though it needs to be applied to a wider recovery time range and a larger number of samples. The suggested condition of testicular failure seen in the subjects of the present study seems to be a temporary condition provoked by the infection with SARS-CoV-2 virus, since levels of the tested hormones were closer to their normal/or appropriately normal values as the recovery period from COVID-19 was increased. As seen from the results, the abnormality in levels of the hormones reflecting the condition of testicular failure was more pronounced in the recently recovered subjects (3 months recovery group), while their levels were closer to the normal range in the long term recovered subjects (7 months recovery group).

Conclusions. Serum testosterone levels were significantly lower in the COVID-19 recovered subjects and were positively associated with the recovery period. Serum LH, FSH and prolactin levels were significantly higher in the COVID-19 recovered subjects, and their levels were negatively associated with the recovery period. The infection with SARS-CoV-2 may have an impact on the levels of sex and fertility hormones in males of reproductive age. Thus, COVID-19 may cause a temporary condition of testicular failure that may improve as the recovery period from the infection increases.

Conflct of interest. Authors have completed the Unified Conflicts of Interest form at http://ukr-biochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

Funding. This research did not receive any funding from any official, commercial or noncommercial organizations and it was solely funded by the private contribution of the authors.

Acknowledgment. The work was supported by the Department of Molecular and Medical Biotechnology, College of Biotechnology, Al-Nahrain University, Jadriya, Baghdad, Iraq.

РІВЕНЬ СТАТЕВИХ ГОРМОНІВ ТА ГОРМОНІВ ФЕРТИЛЬНОСТІ В СИРОВАТЦІ КРОВІ ПАЦІЄНТІВ ЧОЛОВІЧОЇ СТАТІ, ЯКІ ОДУЖАЛИ ВІД COVID-19

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Новий коронавірус 2 тяжкого гострого респіраторного синдрому (SARS-CoV-2), що спричинив пандемію COVID-19, є інфекцією широкого спектру дії, яка, окрім дихальних шляхів, може вражати різні органи, зокрема, органи травної, серцево-судинної та сечової систем. Однак негативні ефекти SARS-CoV-2 на чоловічу репродуктивну систему здебільшого ігноруються. Метою цього дослідження було з'ясувати, вплив SARS-CoV-2 на продукування гормонів, які є маркерами чоловічої репродуктивної функції та фертильності. Учасників дослідження (350 осіб чоловічої статі) було розділено на дві групи: 150 пацієнтів з середнім віком 32 ± 7,9, які одужали від COVID-19, а діагноз COVID-19 був підтверджений методом ПЛР, і 200 практично здорових чоловіків-добровольців аналогічного віку. Група пацієнтів була додатково розділена на три групи залежно від періоду одужання - 3, 5 і 7 місяців. Рівні тестостерону, лютеїнізуючого гормону (ЛГ), фолікулостимулюючого гормону (ФСГ) та пролактину в сироватці крові визначали за допомогою автоматичного хемілюмінесцентного аналізатора Mindray CL-1000i. При порівнянні показників пацієнтів, які одужали від COVID-19, з контрольною групою, встановлено зниження рівня тестостерону, що позитивно асоціюється з періодом одужання, та підвищення рівнів ЛГ, ФСГ і пролактину, що негативно асоціюється з періодом одужання. Припускається, що інфікування SARS-CoV-2 може супроводжуватися тимчасовим порушенням функції яєчок.

Ключові слова: статеві гормони, чоловіча фертильність, SARS-CoV-2.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020; 382(8): 727-733.
2. Lake MA. What we know so far: COVID-19 current clinical knowledge and research. *Clin Med (Lond).* 2020; 20(2): 124-127.
3. Yuen KS, Ye ZW, Fung SY, Chan CP, Jin DY. SARS-CoV-2 and COVID-19: The most important research questions. *Cell Biosci.* 2020; 10: 40.
4. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses - drug discovery and therapeutic options. *Nat Rev Drug Discov.* 2016; 15(5): 327-347.
5. Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). *Indian J Pediatr.* 2020; 87(4): 281-286.
6. Chan JF, Lau SK, Woo PC. The emerging novel Middle East respiratory syndrome coronavirus: the "knowns" and "unknowns". *J Formos Med Assoc.* 2013; 112(7): 372-381.
7. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020; 181(2): 271-280.
8. Zhao Y, Zhao Z, Wang Y , Zhou Y, Ma Y, Zuo W. Single-Cell RNA Expression Profiling of ACE2, the Receptor of SARS-CoV-2. *Am J Respir Crit Care Med.* 2020; 202(5): 756-759.
9. Fan C, Lu W , Li K, Ding Y, Wang J. ACE2 Expression in Kidney and Testis May Cause Kidney and Testis Infection in COVID-19 Patients. *Front Med (Lausanne).* 2021; 7: 563893.

10. Wang Z, Xu X. scRNA-seq Profiling of Human Testes Reveals the Presence of the ACE2 Receptor, A Target for SARS-CoV-2 Infection in Spermatogonia, Leydig and Sertoli Cells. *Cells*. 2020; 9(4): 920.
11. Chai X, Hu L, Zhang Y, Han W, Zhou L, Ke A, Zhou J, Shi G, Fang N, Fan J, Cai J, Fan J, Lan F. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. *bioRxiv*. 2020.
12. Zhang H, Kang Z, Gong H, Xu D, Wang J, Li Z, Li Z, Cui X, Xiao J, Zhan J Meng T, Zhou W, Liu J, Xu H. Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process. *Gut*. 2020; 69(6): 1010-1018.
13. Ng SC, Tilg H. COVID-19 and the gastrointestinal tract: more than meets the eye. *Gut*. 2020;69(6): 973-974.
14. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020; 14(2): 185-192.
15. Bird BM, Zilioli S. Testosterone. In: Encyclopedia of Evolutionary Psychological Science. Eds. Weekes-Shackelford VA, Shackelford TK. Cham: Springer International Publishing AG; 2017. p. 1-3.
16. Ilahi S, Ilahi TB. Anatomy, Adenohypophysis (Pars Anterior, Anterior Pituitary). In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
17. Ulloa-Aguirre A, Reiter E , Crépieux P. FSH Receptor Signaling: Complexity of Interactions and Signal Diversity. *Endocrinology*. 2018; 159(8): 3020-3035.
18. Lucas BK, Ormandy CJ, Binart N, Bridges RS, Kelly PA. Null mutation of the prolactin receptor gene produces a defect in maternal behavior. *Endocrinology*. 1998; 139(10): 4102-4107.
19. Albertson BD, Sienkiewicz ML, Kimball D, MunabiAK, Cassorla F, Loriaux DL. New evidence for a direct effect of prolactin on rat adrenal steroidogenesis. *Endocr Res*. 1987; 13(3): 317-333.
20. Bartke A. Hyperprolactinemia and male reproduction. In: Paulson J, Negro-Vilar A, Lucena E, Martini L (eds.). Andrology: Male Fertility and Sterility. New York: Academic Press; 1986; 101-123.
21. Liu W, Han R, Wu H, Han D. Viral threat to male fertility. *Andrologia*. 2018; 50(11): e13140.
22. Xu J, Qi L, Chi X, Yang J, Wei X, Gong E, Peh S, Gu J. Orchitis: a complication of severe acute respiratory syndrome (SARS). *Biol Reprod*. 2006; 74(2): 410-416.
23. Esteves SC. Clinical management of infertile men with nonobstructive azoospermia. *Asian J Androl*. 2015; 17(3): 459-470.
24. Sokol RZ, Swerdloff RS. Endocrine evaluation. In: Infertility in the male. Eds. Lipshultz LI, Howards SS. 3rd ed. New York: Churchill Livingstone; 1997. p. 210-218.
25. Bhasin S, de Kretser DM, Baker HW. Clinical review 64: Pathophysiology and natural history of male infertility. *J Clin Endocrinol Metab*. 1994; 79(6): 1525-1529.
26. Forti G, Krausz C. Clinical review 100: Evaluation and treatment of the infertile couple. *J Clin Endocrinol Metab*. 1998; 83(12): 4177-4188.
27. Baker HWG. Male infertility. In: Endocrinology. Eds. DeGroot LG, Jameson JL. 4th ed. Philadelphia: Saunders Company; 2001. p. 3199-3228.
28. Albertson BD, Sienkiewicz ML, Kimball D, Munabi AK, Cassorla F, Loriaux DL. New evidence for a direct effect of prolactin on rat adrenal steroidogenesis. *Endocr Res*. 1987; 13(3): 317-333.
29. Smith MS, Bartke A. Effects of hyper-prolactinemia on the control of luteinizing hormone and follicle-stimulating hormone secretion in the male rat. *Biol Reprod*. 1987; 36(1): 138-147.
30. Rasmussen DD. The interaction between mediobasohypothalamic dopaminergic and endorphinergic neuronal systems as a key regulator of reproduction: an hypothesis. *J Endocrinol Invest*. 1991; 14(4): 323-352.
31. Ramesh Babu S, Sadhnani MD, Swarna M, Padmavathi P, Reddy PP. Evaluation of FSH, LH and testosterone levels in different subgroups of infertile males. *Indian J Clin Biochem*. 2004; 19(1): 45-49.
32. Rastrelli G, Di Stasi V, Inglese F, Beccaria M, Garuti M, Di Costanzo D, Spreafico F, Greco GF, Cervi G, Pecoriello A, Magini A, Todisco T, Cipriani S, Maseroli E, Corona G, Salonia A, Lenzi A, Maggi M, De Donno G, Vignozzi L. Low testosterone levels predict clinical adverse

outcomes in SARS-CoV-2 pneumonia patients. *Andrology*. 2021; 9(1): 88-98.

33. Schroeder M, Schaumburg B, Mueller Z, Parplys A, Jarczak D, Roedl K, Nierhaus A, de Heer G, Grensemann J, Schneider B, Stoll F, Bai T, Jacobsen H, Zickler M, Stanelle-Bertram S, Klaetschke K, Renné T, Meinhardt A, Aberle J, Hiller J, Peine S, Kreienbrock L, Klingel K, Kluge S, Gabriel G. High estradiol and low testosterone levels are associated with critical illness in male but not in female COVID-19 patients: a retrospective cohort study. *Emerg Microbes Infect*. 2021; 10(1): 1807-1818.