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SEX HORMONE PROFILES IN PREPUBERTAL AND PUBERTAL CHILDREN WITH SARS-COV-2 INFECTION AND MULTISYSTEM INFLAMMATORY SYNDROME

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Summary.

Sex hormones not only influence the severity of SARS-CoV-2 infection, but can also be direct targets of viral damage. However, in the pediatric population, hormone level assessment was not included in COVID-19 management protocols, resulting in insufficient understanding of hormonal profile alterations during SARS-CoV-2 infection and multisystem inflammatory syndrome in children (MIS-C).

This study aimed *to investigate the features of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and estradiol levels in prepubertal and pubertal children infected with SARS-CoV-2.*

Materials and methods. *A total of 123 children with COVID-19, 32 patients with MIS-C, and 25 healthy SARS-CoV-2-negative children aged 1-17 years were examined. Hormone levels were determined using the AccuBind ELISA Kit (Monobind Inc., Lake Forest, CA, USA). The study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Bioethics Committee of I. Horbachevsky Ternopil National Medical University, Ministry of Health of Ukraine (Protocol No. 71, dated 25 October 2022).Statistical analysis was performed using IBM SPSS Statistics 21.0 and GraphPad Prism 8.4.3.*

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Results. *In boys with COVID-19, a significant decrease in LH and testosterone levels was observed during puberty, as well as lower testosterone levels in the prepubertal period compared to healthy peers. In boys with MIS-C, LH, FSH, and testosterone levels were reduced in both prepubertal and pubertal groups. Despite a statistically significant decrease relative to controls, testosterone levels remained within reference ranges. In girls with COVID-19, FSH levels were reduced during the prepubertal period, and both LH and FSH were decreased during puberty. In contrast, MIS-C was associated with a progressive decline in gonadotropin concentrations. Compared to reference values, a significantly higher frequency of reduced FSH levels was observed in COVID-19 (13.43%) and MIS-C (25.00%), as well as elevated FSH levels in MIS-C (18.75%), compared with the control group ($p<0.05$) in prepubertal age. One-third of adolescents with MIS-C (31.25%) had reduced FSH levels, which was not seen in the control group ($p < 0.05$)*

Conclusions*. The course of COVID-19 and MIS-C in children is associated with dysfunction of the hypothalamic–pituitary–gonadal axis, which should be considered during clinical follow-up and management of patients after recovery.*

Keywords: *Luteinizing Hormone; Follicle-Stimulating Hormone; Testosterone; Estradiol; COVID-19; MIS-C; Children.*

Introduction

One of the key determinants of the clinical course of coronavirus disease, in both children and adults, is the multifaceted pathophysiological impact of SARS-CoV-2, mediated by the widespread expression of the angiotensin-converting enzyme 2 (ACE2) receptor. A considerable number of human tissues and organs express ACE2, including components of the endocrine system. This is particularly relevant, as ACE2 receptors have been identified in multiple endocrine structures – namely, the testes, ovaries, pituitary gland, hypothalamus, adrenal glands, thyroid gland, and pancreas [1-3]. These findings suggest that SARS-CoV-2 may disrupt endocrine homeostasis, including the secretion of sex hormones, either through direct cytopathic effects on gonadal or central endocrine structures (hypothalamus and pituitary gland) or indirectly via systemic inflammatory responses [4, 5].

Studies in adult populations have demonstrated that, despite comparable incidence rates of COVID-19 between sexes, males are nearly three times more likely to require admission to intensive care units (odds ratio = 2.85) and exhibit an elevated risk of mortality (1.39-2.4-fold) relative to females [1, 6, 7]. In contrast, among prepubertal children, no significant sex-based differences in susceptibility to infection or mortality have been reported [1, 8]. In adult males with severe COVID-19, reduced testosterone concentrations have been observed compared with those exhibiting mild disease; however, the directionality of this association remains uncertain – namely, whether low testosterone represents a consequence of severe illness or a predisposing factor [1, 9, 10]. Conversely, estrogen has been shown to exert protective immunomodulatory effects, and low concentrations have been associated with unfavourable outcomes [1, 11].

It has been established that SARS-CoV-2 may affect structures of the hypothalamic–pituitary–gonadal axis, potentially resulting in alterations in luteinising hormone (LH) and follicle-stimulating hormone (FSH) secretion. Nevertheless, reported findings remain inconsistent: some investigations describe elevated concentrations of these gonadotropins, whereas others report diminished levels [12, 13].

Sex-based differences in the progression of COVID-19 have also been attributed to the modulatory actions of sex hormones, which may influence both susceptibility to infection and the severity of acute respiratory distress syndrome [14, 15]. This is attributable to the role of sex hormones in regulating immune responses. For instance,

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estrogen activates estrogen receptors, thereby enhancing type I interferon production and promoting antiviral defence mechanisms [16, 17]. In contrast, testosterone exerts immunosuppressive effects, attenuating dendritic cell activity – the principal source of type I interferons [16, 17].

Although these patterns have been extensively characterised in adults, they remain largely unexplored in paediatric populations. The COVID-19 pandemic has drawn attention to potential endocrine sequelae in childhood; notably, an increased incidence of central precocious puberty, predominantly in females, has been documented [18-20]. This observation suggests a possible impact of SARS-CoV-2 infection on the hypothalamic–pituitary–gonadal axis and, consequently, on circulating sex hormone concentrations.

Therefore, it is essential not only to consider the potential influence of sex hormones on the clinical course of COVID-19 and multisystem inflammatory syndrome in children (MIS-C), but also to acknowledge that these hormones may themselves be targets of viral pathogenic effects. However, in paediatric populations, assessment of sex hormone concentrations is not routinely incorporated into standard clinical management protocols, resulting in a paucity of evidence on this subject.

This study aimed to investigate the features of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and estradiol levels in prepubertal and pubertal children infected with SARS-CoV-2.

Materials and Methods

A total of 123 children with laboratory-confirmed coronavirus disease 2019 (COVID-19) and 32 patients diagnosed with multisystem inflammatory syndrome in children (MIS-C), all hospitalised in facilities in Ternopil, were enrolled in the study. An additional 25 SARS-CoV-2-negative children served as the control group. The diagnosis of MIS-C was established in accordance with the criteria issued by the World Health Organization [21].

The study population comprised children aged 1-17 years. Clinical evaluation included pubertal staging according to the Tanner scale. Of the total cohort, 95 children were prepubertal (Tanner stage 1) and 85 were pubertal. No significant differences in sex distribution were observed between the prepubertal and pubertal subgroups ($p > 0.05$). Among prepubertal participants, 55 were male (57.89%) and 40 were female (42.11%); among pubertal participants, 53 were male (62.35%) and 32 were female (37.65%).

Serum concentrations of sex hormones were quantified using AccuBind ELISA Kits (Monobind Inc., Lake Forest, CA 92630, USA): Estradiol (E_2) Test System (Product Code: 4925-300), Testosterone Test System (Product Code: 3725-300), Luteinising Hormone (LH) Test System (Product Code: 625-300), and Follicle-Stimulating Hormone (FSH) Test System (Product Code: 425-300). Venous blood samples were obtained on the first day of hospitalisation, prior to the initiation of any therapeutic interventions. Results were interpreted using age-, sex-, and Tanner stage–specific reference intervals [22, 23].

Written informed consent was obtained from all parents or legal guardians. The study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Bioethics Committee of I. Horbachevsky Ternopil National Medical University, Ministry of Health of Ukraine (Protocol No. 71, dated 25 October 2022).

Statistical analyses were performed using IBM SPSS Statistics, version 21.0, and GraphPad Prism, version 8.4.3. Owing to the non-normal distribution of quantitative variables, data are expressed as median and interquartile range (Median [LQ; UQ]). Intergroup comparisons of quantitative variables across the three cohorts were conducted using the Kruskal–Wallis test. Categorical variables are presented as absolute frequencies (n) and percentages (%); 3 × 2 contingency tables were analysed using Pearson's chi-squared (χ^2) test. A p-value of less than 0.05 was considered statistically significant.

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Results and Discussion

Analysis of sex hormone concentrations in prepubertal and pubertal children revealed alterations in gonadotrophin secretion – specifically, luteinising hormone (LH) and follicle-stimulating hormone (FSH) – during acute SARS-CoV-2 infection and multisystem inflammatory syndrome in children (MIS-C), relative to healthy, age- and sex-matched SARS-CoV-2-negative controls.

In prepubertal males, a significant reduction in LH concentrations was observed in the MIS-C group compared with the control group. A comparable reduction was noted in pubertal males, with lower LH levels in both the MIS-C and acute COVID-19 groups ($p < 0.05$) (Figure 1). In prepubertal females, no significant intergroup differences in LH levels were detected; however, during late puberty, LH concentrations were significantly diminished in both COVID-19 and MIS-C patients relative to uninfected peers ($p < 0.05$) (Figure 2).

FSH levels were significantly reduced in pubertal males with MIS-C (Tanner stages 3-4) ($p < 0.05$). Although no statistically significant differences were found between the control group and patients with acute COVID-19, FSH concentrations in the latter remained significantly higher than those in the MIS-C group ($p < 0.05$) (Figure 1). In females, FSH levels differed from those of controls in both the prepubertal and pubertal periods. Prepubertal girls infected with SARS-CoV-2 exhibited a significant decrease in FSH concentrations ($p < 0.05$) (Figure 2). In the COVID-19 group, FSH levels declined at Tanner stage 2, with further reductions observed in both the COVID-19 and MIS-C groups during late puberty compared with controls ($p < 0.05$) (Figure 2). In MIS-C, FSH suppression was more pronounced, with values significantly lower than those in both the control group and the COVID-19 group ($p < 0.05$) (Figure 2).

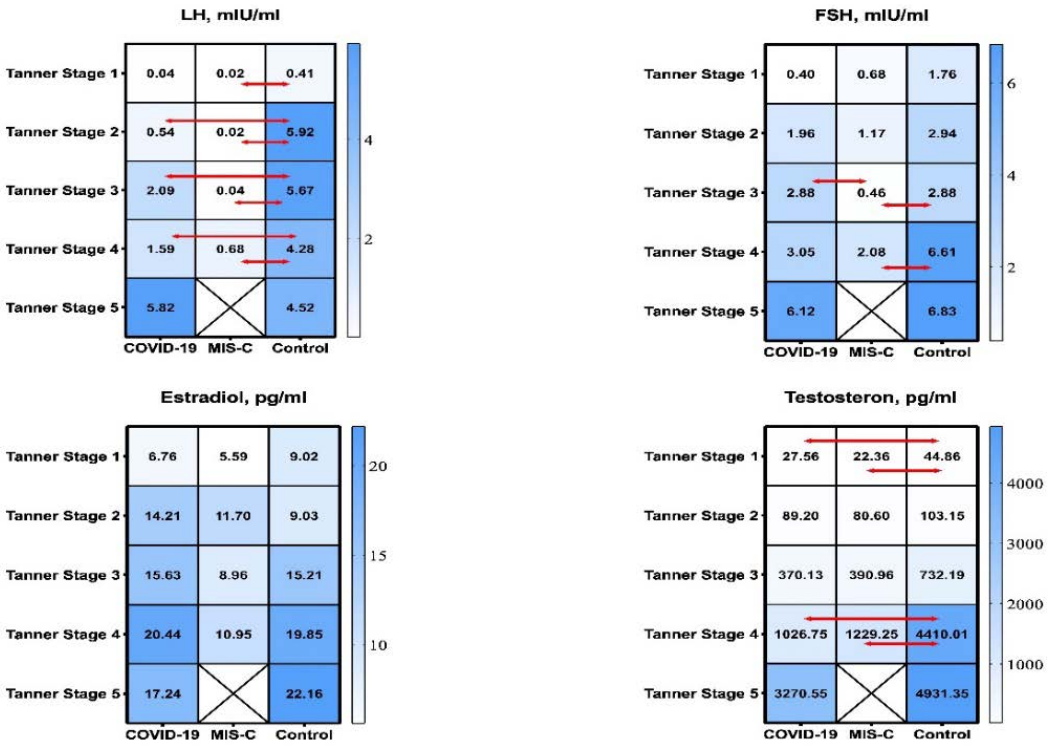

Figure 1. Serum concentrations of luteinising hormone (LH), follicle-stimulating hormone (FSH), estradiol, and testosterone in males with coronavirus disease 2019 (COVID-19), multisystem inflammatory syndrome in children (MIS-C), and controls, stratified by Tanner stage of pubertal development. (↔ statistically significant difference between groups, p < 0.05).

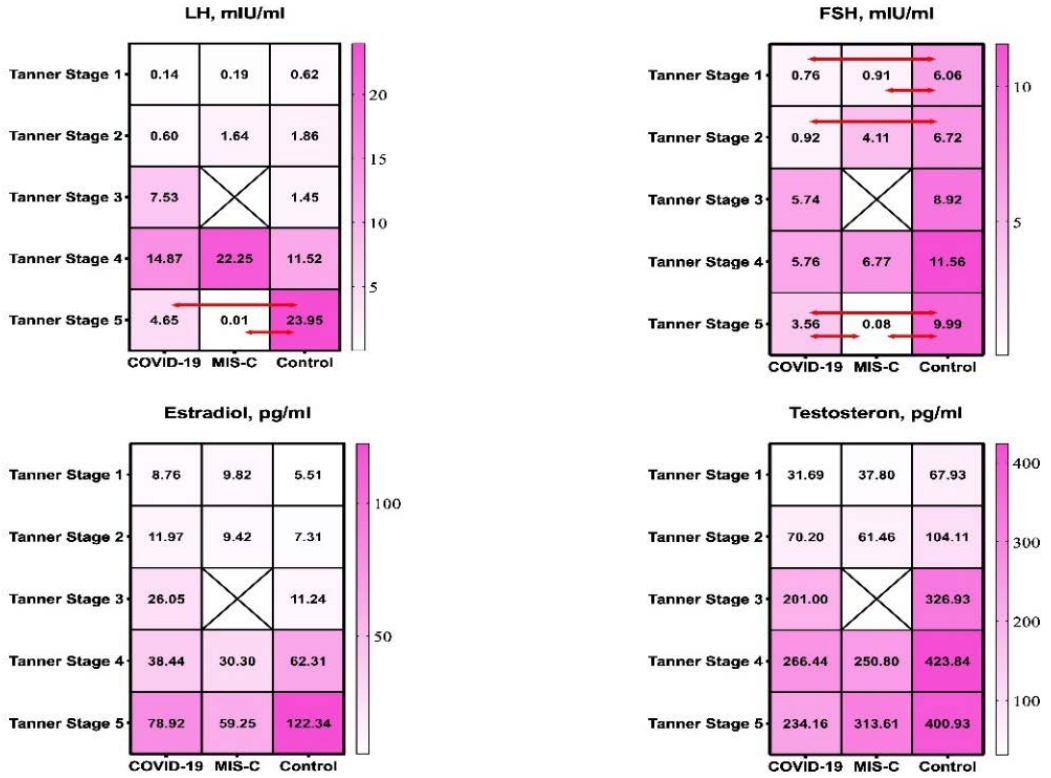

Figure 2. Serum concentrations of luteinising hormone (LH), follicle-stimulating hormone (FSH), estradiol, and testosterone in females with coronavirus disease 2019 (COVID-19), multisystem inflammatory syndrome in children (MIS-C), and controls, stratified by Tanner stage of pubertal development. (↔ statistically significant difference between groups, p < 0.05)

Estradiol concentrations did not differ significantly among children with COVID-19, those with MIS-C, and healthy controls, irrespective of sex or pubertal stage ($p > 0.05$) (Figures 1 and 2). Similarly, testosterone levels in females showed no significant intergroup variation ($p > 0.05$) (Figure 2). In contrast, males demonstrated

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a substantial reduction in total testosterone concentrations in both the prepubertal and pubertal periods, most notably at Tanner stage 4 ($p < 0.05$) (Figure 1).

Comparative analysis indicated that estradiol and testosterone levels generally remained within age-specific reference intervals, whereas gonadotrophin concentrations (LH and FSH) exhibited notable deviations. Specifically, prepubertal children with COVID-19 displayed elevated LH levels not observed in healthy peers; however, the intergroup difference did not reach statistical significance ($\chi^2 = 4.18$; $p = 0.124$) (Table 1). In prepubertal children with MIS-C, the proportion of individuals with elevated FSH levels was increased (18.75%), whereas in those with COVID-19, reductions in FSH were more prevalent (13.43%) (Table 1).

Table 1

Analysis of luteinising hormone (LH) and follicle-stimulating hormone (FSH) concentrations in prepubertal children with COVID-19, multisystem inflammatory syndrome in children (MIS-C), and controls (SARS-CoV-2-negative children) (%)

Parameter	Hormone Level	COVID-19	MIS-C	Control	χ^2, p
Luteinizing hormone (LH)	Age-appropriate	94.03	81.25	100.00	χ^2=4.18; p=0.124
	Decreased	–	–	–	
	Increased	5.97	6.25	0.00	
Follicle-stimulating hormone (FSH)	Age-appropriate	85.07	56.25	100.00	χ^2=14,70; p=0,005*
	Decreased	13.43	25.00	0.00	
	Increased	1.49	18.75	0.00	

Note 1. χ^2 – Pearson's chi-square test and corresponding p-value.
*Note 2. * – statistically significant difference ($p < 0.05$).*

During puberty, patients with both COVID-19 and MIS-C exhibited both diminished and elevated LH values, although no statistically significant differences were detected relative to the control group (Table 2). One-third of adolescents with MIS-C (31.25%) exhibited reduced FSH levels – a finding absent in the control group ($p < 0.05$) (Table 2).

Table 2

Analysis of luteinising hormone (LH) and follicle-stimulating hormone (FSH) concentrations in pubertal children with COVID-19, multisystem inflammatory syndrome in children (MIS-C), and controls (SARS-CoV-2-negative children) (%)

Parameter	Hormone Level	COVID-19	MIS-C	Control	χ^2, p
Luteinizing hormone (LH)	Age-appropriate	89.09	81.25	100.00	χ^2=4,16; p=0,385
	Decreased	3.64	12.50	0.00	
	Increased	7.27	6.25	0.00	
Follicle-stimulating hormone (FSH)	Age-appropriate	90.91	62.50	100.00	χ^2=11,41; p=0,022*
	Decreased	7.27	31.25	0.00	
	Increased	1.82	6.25	0.00	

Note 1. χ^2 – Pearson's chi-square test and corresponding p-value.
*Note 2. * – statistically significant difference ($p < 0.05$).*

The findings of the present study are consistent with those reported in previous meta-analyses. For instance, a meta-analysis of eight cohort studies revealed that testosterone concentrations in adult males with COVID-19 were significantly lower than those in uninfected controls. Concurrently, LH and FSH levels exhibited a tendency toward elevation, although this trend did not attain statistical significance [24]. A further meta-analysis encompassing 18 studies (n = 1575) corroborated a reduction in testosterone levels in patients with severe COVID-19 relative to those with mild disease and to healthy controls [14]. The lowest testosterone concentrations were documented in individuals with fatal outcomes of COVID-19 [14, 25].

These observations suggest that the decline in testosterone levels in paediatric patients may not be attributable solely to the direct cytopathic effects of SARS-CoV-2 on Leydig cells – which express both transmembrane serine protease 2 (TMPRSS2) and angiotensin-converting enzyme 2 (ACE2) receptors – but may also reflect the systemic physiological response to critical illness. The inflammatory cascade, cytokine release, pyrexia, and metabolic perturbations may collectively contribute to reduced testosterone synthesis [14, 24, 26]. Furthermore, dysfunction of the hypothalamic–pituitary–gonadal (HPG) axis and impaired androgen receptor responsiveness under conditions of stress and inflammation may also be implicated [26]. It is noteworthy that SARS-CoV-2 possesses the capacity to directly infect gonadal tissue, targeting Leydig and Sertoli cells via TMPRSS2- and ACE2-mediated entry, potentially resulting in functional gonadal impairment [14].

Meta-analytical evidence has indicated a trend toward diminished estradiol concentrations in individuals with COVID-19, a phenomenon more pronounced in females. This supports the hypothesis that estrogens may exert a protective effect [26]. Estrogens have been shown to downregulate ACE2 expression in bronchial epithelial cells and airway smooth muscle, and to interfere with

the interaction between glycosylated ACE2 and the SARS-CoV-2 spike protein, thereby impeding viral cellular entry [27].

A meta-analysis of 12 studies (n = 3257) did not identify statistically significant alterations in FSH levels between infected and non-infected individuals. However, a meta-analysis of 13 studies (n = 3288) reported a trend toward elevated LH concentrations, particularly in individuals under 50 years of age. The authors highlighted the potential influence of stress and inflammatory mediators on HPG axis dysregulation [26].

In the present study, alterations in gonadotrophin and testosterone concentrations were observed, indicating a potential risk of disruption to the physiological trajectory of pubertal development in children infected with SARS-CoV-2. Specifically, sporadic elevations in LH and FSH in prepubertal children may reflect premature activation of the HPG axis, possibly predisposing to central precocious puberty. Conversely, reductions in LH, FSH, and testosterone observed in COVID-19 – particularly in MIS-C – may signify a risk of hypogonadotropic hypogonadism and consequent delay in pubertal progression. Although no overt clinical signs of pubertal disorders were detected in the studied cohort, the identified hormonal deviations suggest a transient impairment of hypothalamic–pituitary–gonadal axis function secondary to SARS-CoV-2 infection.

Conclusions

Coronavirus disease 2019 (COVID-19) has been demonstrated to exert a significant influence on sex hormone concentrations in males during puberty, characterised by reduced levels of LH and testosterone. A comparable effect was observed during the prepubertal period, with boys exhibiting lower testosterone concentrations relative to healthy controls. In males with MIS-C, a post-infectious complication associated with SARS-CoV-2, reductions in LH, FSH, and testosterone were evident in both prepubertal and pubertal subgroups. Similarly, females with COVID-19 displayed diminished FSH levels during the prepubertal period and reductions in both LH and FSH during adolescence. In girls with MIS-C, a progressive decline in gonadotrophin concentrations (LH and FSH) was noted. These findings indicate that both COVID-19 and MIS-C may disrupt the normal regulatory function of the hypothalamic–pituitary–gonadal axis in paediatric patients. Consequently, this potential endocrine dysfunction should be taken into account during long-term clinical follow-up and post-recovery management.

Perspectives for Future Research

The alterations in sex hormone profiles observed during acute SARS-CoV-2 infection and multisystem inflammatory syndrome in children underscore the necessity for further investigation into the functional status of the hypothalamic–pituitary–gonadal axis during systemic inflammatory illness, particularly in severe cases. Inclusion of a larger, more diverse cohort – encompassing both sexes and the full spectrum of pubertal stages – would facilitate a more comprehensive characterisation of infection-related endocrine disturbances and support the development of evidence-based strategies for monitoring and managing hormonal imbalances in affected children.

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ПРОФІЛІ СТАТЕВИХ ГОРМОНІВ У ДІТЕЙ ПРЕПУБЕРТАТНОГО ТА ПУБЕРТАТНОГО ВІКУ ПРИ ІНФЕКЦІЇ SARS-COV-2 ТА МУЛЬТИСИСТЕМНОМУ ЗАПАЛЬНОМУ СИНДРОМІ

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(м. Тернопіль, Україна)**

Резюме.

Статеві гормони не лише впливають на тяжкість перебігу інфекції SARS-CoV-2, але й самі можуть бути мішенню для вірусного ураження. Водночас у дитячій популяції їх визначення не входило до протоколів менеджменту COVID-19, що зумовило недостатню вивченість змін гормонального профілю при SARS-CoV-2 та мультисистемному запальному синдромі у дітей (MIS-C).

Мета дослідження: вивчити особливості рівнів лютеїнізуючого гормону (ЛГ), фолікулостимулюючого гормону (ФСГ), тестостерону та естрадіолу у дітей препубертатного та пубертатного віку, інфікованих вірусом SARS-CoV-2.

Матеріали і методи дослідження. Обстежено 123 дитини із COVID-19, 32 пацієнти із MIS-C та 25 здорових дітей, не інфікованих вірусом SARS-CoV-2, віком 1-17 років. Рівні гормонів визначали за допомогою тест-систем AccuBind ELISA Kit (Monobind Inc., Lake Forest, CA 92630, USA). Дослідження схвалено комісією з біоетики Тернопільського національного медичного університету ім. І. Я. Горбачевського Міністерства охорони здоров'я України (Протокол № 71 від 25 жовтня 2022 року). Статистичний аналіз проведено з використанням програм IBM SPSS Statistics 21.0 та GraphPad Prism 8.4.3.

Науково-дослідна робота «Оптимізація діагностики клініко-патогенетичних характеристик коронавірусної інфекції COVID-19 у дітей з коморбідною патологією та особливості лікування», УДК: 616.98:578.834.1-06-071-08-053.2б № держ. реєстрації 0123U100064, терміни виконання – 2023-2025 роки.

Результати дослідження. У хлопчиків із COVID-19 відзначено достовірне зниження рівнів ЛГ та тестостерону у пубертатному віці, а також тестостерону у препубертатному періоді порівняно зі здоровими однолітками. Для MIS-C у хлопчиків характерне зниження рівнів ЛГ, ФСГ і тестостерону як у препубертатному, так і пубертатному віці. Попри статистично значуще зниження рівня тестостерону відносно контролю його показники залишалися у межах референтних норм. У дівчаток із COVID-19 спостерігалося зниження ФСГ у препубертатному віці та ЛГ і ФСГ у пубертатному періоді, тоді як при MIS-C відзначено прогресивне зниження концентрацій гонадотропінів. Порівняльний аналіз відносно референтних значень продемонстрував достовірно вищу частоту зниженого рівня ФСГ при COVID-19 (13,43%) і MIS-C (25,00%), а також підвищеного рівня ФСГ при MIS-C (18,75%) порівняно з контролем у препубертатному віці ($p<0,05$). Третина підлітків з MIS-C (31,25%) характеризувалася зниженим рівнем ФСГ, що не було властивим для контрольної групи ($p<0,05$)

Висновки. Перебіг COVID-19 та MIS-C у дітей асоціюється із дисфункцією гіпоталамо-гіпофізарно-гонадної осі, що варто враховувати при клінічному спостереженні та подальшому менеджменті пацієнтів після перенесених форм захворювання.

Ключові слова: лютеїнізуючий гормон; фолікулостимулюючий гормон; тестостерон; естрадіол; COVID-19; MIS-C; діти.

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