

SERUM PHOSPHOLIPID AND SELECTED OXYLIPIN LEVELS IN SECOND-TRIMESTER PREGNANT WOMEN WITH COVID-19

Ishutina N.A.,
Andrievskaya I.A.

Far Eastern Scientific Centre of Physiology
and Pathology of Respiration
(Kalinina str., 22, Blagoveshchensk 675000,
Russian Federation)

Corresponding author:
Natali A. Ishutina,
e-mail: ishutina-na@mail.ru

RESUME

Background. The inflammatory response in coronavirus disease 2019 (COVID-19) markedly alters lipid metabolism. However, the phospholipid and oxylipin profile of pregnant women with COVID-19, stratified by disease severity, remains insufficiently studied.

The aim. To assess second-trimester serum levels of phospholipids, arachidonic acid, and the oxylipins 12- and 15-hydroxyeicosatetraenoic acids (12-HETE, 15-HETE) in women with COVID-19 according to clinical severity.

Methods. The study enrolled 88 pregnant women at 14–16 weeks of gestation with confirmed COVID-19. Patients with moderate disease ($n = 42$) formed subgroup 1; those with mild disease ($n = 46$), subgroup 2. A control group comprised 40 second-trimester pregnant women without COVID-19. Serum phospholipids were quantified by thin-layer chromatography; 12-HETE and 15-HETE by enzyme-linked immunosorbent assay; and arachidonic acid by gas–liquid chromatography.

Results. Compared with the mild-disease subgroup, women with moderate COVID-19 and control group showed significantly higher serum concentrations of sphingomyelin, lysophosphatidylcholine, arachidonic acid, 12-HETE, and 15-HETE, and lower levels of phosphatidylcholine and phosphatidylethanolamine ($p < 0.001$ for all comparisons).

Conclusion. The development of COVID-19 in second-trimester pregnant women is associated with severity-dependent alterations in serum phospholipids, arachidonic acid, and oxylipins. These changes may reflect the intensity of pulmonary inflammation and underscore the need to optimise therapeutic approaches in this patient population.

Keywords: COVID-19, pregnancy, phospholipids, arachidonic acid, 12-hydroxyeicosatetraenoic acid, 15-hydroxyeicosatetraenoic acid

Received: 03.06.2025
Accepted: 08.10.2025
Published: 26.11.2025

For citation: Ishutina N.A., Andrievskaya I.A. Serum phospholipid and selected oxylipin levels in second-trimester pregnant women with COVID-19. *Acta biomedica scientifica*. 2025; 10(5): 114-121. doi: 10.29413/ABS.2025-10.5.13

ПОКАЗАТЕЛИ ФОСФОЛИПИДОВ И НЕКОТОРЫХ ОКСИЛИПИНОВ В СЫВОРОТКЕ КРОВИ БЕРЕМЕННЫХ С COVID-19 ВО ВТОРОМ ТРИМЕСТРЕ

**Ишутина Н.А.,
Андриевская И.А.**

Федеральное государственное
бюджетное научное учреждение
«Дальневосточный научный центр
физиологии и патологии дыхания» (ДНЦ
ФПД) (675000, г. Благовещенск,
ул. Калинина, 22, Россия)

Автор, ответственный за переписку:
**Ишутина Наталия
Александровна,**
e-mail: ishutina-na@mail.ru

РЕЗЮМЕ

Обоснование. Воспалительный процесс при COVID-19 значительно модифицирует метаболизм липидов. Однако состав фосфолипидов и оксипинов у беременных с COVID-19 в зависимости от тяжести течения заболевания изучен недостаточно, что актуализирует тематику исследований.

Цель исследования. Дать оценку содержания сывороточных фосфолипидов, арахидоновой кислоты, оксипинов (12- и 15-гидроксиэйкозатетраеновой кислот) во втором триместре у женщин в зависимости от степени тяжести COVID-19.

Методы. В основную группу исследования включены 88 беременных с COVID-19 во втором триместре (14–16 недель). Пациентки со среднетяжелым течением COVID-19 ($n = 42$) составили 1 подгруппу; легким течением ($n = 46$) – 2 подгруппу. Сорок беременных во втором триместре, без COVID-19, вошли в контрольную группу. В крови определяли концентрацию фосфолипидов методом тонкослойной хроматографии; 12- и 15-гидроксиэйкозатетраеновых кислот методом иммуноферментного анализа; арахидоновой кислоты – методом газо-жидкостной хроматографии.

Результаты. При сравнительном анализе результатов исследования было выявлено, что у женщин со среднетяжелым течением COVID-19 по сравнению с легким течением заболевания и контрольной группой в сыворотке крови наблюдались статистически значимо более высокие показатели сфингомиелина, лизофосфатидилхолина, арахидоновой кислоты, 12- и 15-гидроксиэйкозатетраеновых кислот при низких значениях фосфатидилхолина и фосфатидилэтаноламина ($p < 0,001$).

Заключение. Развитие COVID-19 у беременных во втором триместре ассоциировано с изменением содержания фосфолипидов, арахидоновой кислоты и оксипинов в сыворотке крови, зависящее от тяжести патологического процесса. Выявленные нарушения в составе фосфолипидов и оксипинов у беременных с COVID-19 могут потенциально отражать тяжесть течения воспалительного процесса в бронхолегочной системе и диктуют необходимость оптимизации терапевтических подходов в данной группе пациентов.

Ключевые слова. COVID-19, беременность, фосфолипиды, арахидоновая кислота, 12-гидроксиэйкозатетраеновая кислота, 15-гидроксиэйкозатетраеновая кислота

Статья поступила: 03.06.2025
Статья принята: 08.10.2025
Статья опубликована: 26.11.2025

Для цитирования: Ишутина Н.А., Андриевская И.А. Показатели фосфолипидов и некоторых оксипинов в сыворотке крови беременных с COVID-19 во втором триместре. *Acta biomedica scientifica*. 2025; 10(5): 114-121. doi: 10.29413/ABS.2025-10.5.13

BACKGROUND

Lipids and their metabolites have been shown to be a diverse group of molecules involved in regulating inflammation in pulmonary diseases [1], including COVID-19. Lipids play a significant role in the life-cycle of the SARS-CoV-2 virus [2], serving as receptors or facilitating the entry of viruses into cells. They are also involved in viral replication complexes and energy production for efficient viral replication. They regulate the distribution of viral proteins within the cell and play a role in the assembly, transportation, and release of viral particles [3]. In addition, it has been demonstrated that lipid mediators, such as sphingolipids, lysophospholipids, and products of polyunsaturated fatty acid (PUFA) oxidation – oxylipins – can regulate the host immune response to viral infection [2].

Oxylipins are ligands for various receptor systems. They interact with peroxisome proliferator-activated receptors (PPARs), which are involved in the regulation of lipid homeostasis and inflammatory processes [4]. In addition, oxidized fatty acids serve as monocyte adhesion molecules. Lysophosphatidylcholines act as a strong chemoattractant for macrophages and T lymphocytes. They stimulate the expression of adhesion molecules and cytokines while disrupting endothelial function. Therefore, both lysophosphatidylcholines and oxidized fatty acids (oxylipins) are considered inflammatory mediators [5].

Oxylipins are synthesized from PUFAs, which are constituents of phospholipids, via a series of multiple oxidative reactions catalyzed by specific enzymes (cyclooxygenases, lipoxygenases (LOX) or cytochrome P450 monooxygenases). Additionally, enzyme-independent reactions may occur in the presence of reactive oxygen species (ROS) [6]. Pathological conditions associated with inflammation are thought to be linked to an imbalance between ω -3 (eicosapentaenoic and docosahexaenoic) and ω -6 (arachidonic) PUFA levels, leading to the overproduction of pro-inflammatory lipid mediators (ω -6 oxylipin derivatives, such as prostaglandins and hydroxyeicosatetraenoic acid, HETE) and the underproduction of pro-resolution (ω -3 oxylipin derivatives) molecules [4].

The main metabolite generated by 12-LOX is 12-HETE, which plays a role in various biological processes, including platelet activation and GPR31-mediated regulation of pro-inflammatory mediator production [7, 8]. Another oxylipin synthesized as a result of the enzymatic metabolism of arachidonic acid via 15-LOX is 15-HETE, which is generated during periods of hypoxia and exerts an inhibitory effect on sirtuin-mediated apoptosis in smooth muscle cells of the pulmonary artery by increasing the expression of pro-apoptotic proteins, such as Bcl-2 and Bel-xL [9].

There are several studies in the literature examining the impact of SARS-CoV-2 infection on the metabolism of oxylipins produced by LOX. It has been demonstrated that SARS-CoV-2 disrupts the metabolic pathways of arachidonic acid conversion, leading to an imbalance between pro-inflammatory oxylipins (12-HETE

and 20-HETE), and anti-inflammatory oxylipins (epoxyeicosatrienoic acid) [10, 11]. However, these findings were obtained in non-pregnant individuals. Limited information is available on how the severity of COVID-19 affects oxylipin metabolism in pregnant women. These results support the study of lipid mediator roles in the pathogenesis of COVID-19 in pregnant women, depending on the extent of the pathological process.

THE AIM OF THE STUDY

To evaluate the levels of serum phospholipids, arachidonic acid, and oxylipins (12-HETE and 15-HETE) in pregnant women in the second trimester, depending on the severity of COVID-19 infection.

MATERIALS AND METHODS

Study design and setting

A prospective cohort study was conducted among 128 pregnant women who were hospitalized in the pulmonology department of the Blagoveshchensk City Clinical Hospital in the Amur Region. Of these, 88 women with COVID-19 in the second trimester (14-16 weeks gestation) were included in the study group, which was then divided into two subgroups based on the severity of COVID-19: subgroup 1 ($n = 42$) for women with moderate COVID-19 and subgroup 2 ($n = 46$) for women with mild COVID-19. The severity of COVID-19 was determined in accordance with relevant regulatory documents, such as the clinical guidelines "Organization of Medical Care for Pregnant Women, Women in Labor, and Newborns with Novel Coronavirus Infection (COVID-19)", version 5, published on December 28, 2021.

Inclusion criteria for the main study group were: pregnancy in the second trimester (14–16 weeks), confirmed case of COVID-19 infection (U07.1), presence of clinical symptoms of respiratory disease, signs of viral pneumonia (if indicated by computed tomography) for patients in subgroup 1, signed informed consent from participants to participate in the study and publication of its results in open sources, availability and accessibility of medical records for collection of research information, age of reproductive capacity, and singleton pregnancy. Exclusion criteria included: decompensated chronic somatic diseases, HIV infection, malignancies, and mental disorders.

The average age of participants in subgroup 1 was 29.0 (24.0; 33.0) years, and in subgroup 2 it was 31.0 (26.0; 34.0) years. No statistically significant difference was found between the two groups. The two groups were comparable in terms of age.

Thirty-six patients in subgroup 1 (85.71 %) and 39 patients in subgroup 2 (84.78 %) were married. This determined the comparability of the two groups ($p > 0.05$).

The parity of pregnancy among women in both groups did not differ significantly. In subgroup 1, there

were slightly fewer primigravid women compared to subgroup 2, with 18 (42.86 %) and 20 (43.48 %), respectively ($p > 0.05$).

The control group consisted of 40 pregnant women in their second trimester (14–16 weeks) with a negative COVID-19 status who were seen at the antenatal clinic No. 2 of the Blagoveshchensk City Clinical Hospital in the Amur Region. These patients were aged 30.0 (25.0; 34.0) years. Inclusion criteria for the control group required that the women were in their second trimester (14–16 weeks), had a singleton pregnancy, had no history of COVID-19 infection, had negative nasopharyngeal swab test for SARS-CoV-2 at the time of testing, and did not have a history of acute respiratory viral infection at the time of the examination. Exclusion criteria were the same as those for the study group.

ETHICAL REVIEW

The study has been conducted in accordance with the guidelines of the Declaration of Helsinki (2013), and has been approved by the local ethics committee of the Blagoveshchensk Scientific Center for Fundamental Pediatrics and Pedagogical Research (Protocol No. 172, dated October 12, 2021). All participants have provided informed voluntary consent to participate in the study (in accordance with the Federal Law "On the Fundamentals of Protection of Citizens' Health in the Russian Federation" dated November 21, 2011, No. 323-FZ, as amended December 30, 2021).

Study duration, description, and data collection

The study period for data collection and analysis was from 2022 to 2023.

Peripheral venous blood samples were collected for laboratory analysis. Blood was drawn upon admission to the hospital, after COVID-19 infection had been confirmed through medical diagnosis, using venipuncture in the morning, on an empty stomach. Standard vacuum systems without anticoagulants (Guangzhou Improve Medical Instruments Co., Ltd, China) were used to collect the blood samples. Serum was obtained from the collected blood samples by centrifuging them for 15 minutes at a speed of 1500 g, and then stored at -70°C until analysis.

Serum phospholipid levels (% of the total) were determined in peripheral blood samples after preliminary lipid extraction [12] using a thin-layer chromatography method. The resulting lipid extracts were separated into individual phospholipid components on thin-layer silica gel plates (Supelco, Germany). Two-dimensional thin-layer chromatographic analysis and identification of the individual phospholipids were performed using the protocol described by J. Kirchner [13].

Arachidonic acid concentration was measured by gas-liquid chromatography using a Crystal 2000M chromatograph (Russia), equipped with a flame ionization detector. Peaks were counted and identified using the Chromatec Analytic 2.5 software and hardware package (Russia). Quantitative chromatogram analysis was

performed by internal normalization, which involved determining the area of each analyzed component's peak and calculating its relative percentage of the total area of peaks corresponding to higher fatty acids in the sample.

The levels of bioactive metabolites of arachidonic acid (12-HETE and 15-HETE) in serum samples were analyzed using an enzyme-linked immunosorbent assay (ELISA). Laboratory analyses were carried out using Enzo Life Sciences (USA) reagent kits, following the manufacturer's guidelines, on a StatFax 2100 ELISA (USA).

Statistical analysis

Statistical data processing was conducted using the standard IBM SPSS Statistics v.23.0 software (Statistical Package for the Social Sciences, USA). The sample size was not pre-determined. To test whether the observed sample followed a normal distribution, the Kolmogorov – Smirnov and Shapiro – Wilk tests were employed. Quantitative indicators are reported as Me (Q1; Q3), where Me represents the median and Q1 and Q3 denote the first and third quartiles, respectively. Categorical data is presented as proportions, frequencies, and percentages. For paired comparisons of normally distributed quantitative data between independent groups, a Student's *t*-test was utilized. When comparing groups with non-normal distributions, a non-parametric Mann – Whitney U-test was implemented. Null hypotheses were assessed at a critical significance level of 0.05.

RESULTS AND DISCUSSION

Phospholipids and bioactive metabolites derived from (oxylipins) are of significant interest in the context of COVID-19 research. These compounds form the basis for pulmonary surfactant and play a crucial role in inflammation, maintenance of lung cell integrity, and the viral life cycle [14].

Previous studies have demonstrated that SARS-CoV-2 replication during pregnancy is linked to high levels of phospholipase A2 activity, as well as an imbalance in the prooxidant-antioxidant system. This is characterized by a reduction in the total antioxidant capacity of the serum and an increase in oxidative modification products of biomolecules, as indicated by the levels of diene conjugates and TBA-active products, as well as 8-isoprostane. This oxidative stress may contribute to lung damage and may depend on the severity of the condition [15, 16]. These findings suggest that the composition of phospholipids may be affected by the development of this condition.

A comparative analysis of the study findings revealed differences in the quantitative composition of individual phospholipid fractions in the blood serum of women in the control and study groups. The levels of serum phospholipid subclasses varied depending on the severity of COVID-19 symptoms among participants in the study group (Table 1).

In subgroup 1, the median concentrations of phosphatidylcholine (Pc) and phosphatidylethanolamine (Pe) in the blood serum were decreased by 1.5-fold ($p < 0.001$)

and 1.7-fold ($p < 0.001$), respectively, compared to the control group. In subgroup 2, these values were lower than in the control by 1.2-fold ($p < 0.001$) and 1.3-fold ($p < 0.001$), respectively (Table 1). At the same time, the median level of lysophosphatidylcholine (Lpc) increased by 2.3-fold in subgroup 1 ($p < 0.001$), and by 1.7-fold in subgroup 2 ($p < 0.001$) when compared to the corresponding value in the control group (Table 1).

A decrease in the concentrations of Pe and Pc, accompanied by an increase in the Lpc levels in the blood serum of pregnant women with COVID-19, can be attributed to the intensification of lipid peroxidation and oxidative stress in these patients, as previously demonstrated [15, 16]. The oxidative stress observed in COVID-19 patients may contribute to increased phospholipase A2 activity or reduced Lpc reacylation, resulting in a higher concentration of this lipid.

The findings of Kagan V.E. et al. (2017), were completely unexpected, as they demonstrated that Pe, which contains a large number of arachidonic acyl chains, is a target for lipoxygenase. Lipoxygenase oxidizes unsaturated acyl chains to produce cytotoxic lipid hydroperoxides, leading to ferroptosis [17]. Other researchers have also shown that ferroptosis is one of the primary mechanisms of cell death in lungs infected with SARS-CoV-2. This occurs due to impaired iron metabolism regulation, activation of iron-dependent lipid peroxidation, reduction in phospholipid levels containing polyunsaturated acyl "tails", and accumulation of lysophospholipids. In particular, the accumulation of Lpc leads to increased alveolar epithelial permeability, destruction of pulmonary surfactant, and activation of pro-inflammatory processes [18].

According to current research, increased Lpc levels in COVID-19 patients may increase the risk of inflammation by activating NADPH oxidase in human neutrophils [19]. Additionally, lysophospholipids and arachidonic acid can enhance the production of pro-inflammatory

cytokines (IL-8, IL-6, and IL-1 β) in epithelial cells and monocytes, contributing to the development and persistence of the "inflammatory/cytokine storm" in COVID-19 patients [20]. This, in turn, can lead to disturbances in arachidonic acid metabolism, resulting in an imbalance between pro-inflammatory oxylipins such as 15-HETE and 20-HETE [11, 20]. Therefore, these findings suggest a potential pathogenic role for lysophospholipids and arachidonic acid in initiating or exacerbating COVID-19 disease.

A similar pattern of change was observed for sphingomyelin (Sph) with median values in the blood serum of women in subgroup 1 increasing by 1.8-fold ($p < 0.001$), and in subgroup 2 increasing by 1.4-fold ($p < 0.001$), when compared to the same parameter in the control group (Table 1).

According to international studies, Sph is not directly linked to COVID-19. However, Sph is an important component of membrane lipid rafts, play a role in signal transduction and activation of the immune system [21]. Specifically, proteins targeted by (angiotensin-converting enzyme 2 and membrane-associated proteases) are embedded in these lipid rafts and contribute to viral infection [22]. On the other hand, Sph has been the most extensively studied lipid associated with high-density lipoproteins (HDL). HDL with Sph plays a crucial role in the body's immune response, inhibiting the production of cytokines and chemokines by monocytes and macrophages. Additionally, HDL contains various proteins with antioxidant properties, such as paraoxonase 1, apolipoprotein A1 (apoA1), lipoprotein-associated phospholipase, and glutathione peroxidase 3. HDL is also able to inhibit apoptosis in endothelial cells through activation of the Akt/eNOS and apoA1 pathways, as well as sphingosine-1-phosphate [23]. Recent studies have demonstrated that HDL plays a protective role against severe complications of COVID-19 by regulating the immune response and reducing the severity of inflammatory

TABLE 1
CHANGES IN PERIPHERAL-BLOOD CONCENTRATIONS OF PHOSPHOLIPIDS, 12-HETE, 15-HETE, AND ARACHIDONIC ACID IN THE STUDY GROUPS

Parameter	Control group	Main study group	
		Subgroup 1	Subgroup 2
Pc, %	39.49 (36.79; 42.18)	26.82 (25.88; 27.25), $p < 0.001$	34.17 (33.28; 35.05), $p < 0.001$
Lpc, %	5.29 (5.0; 5.55)	12.0 (11.56; 12.48), $p < 0.001$	8.79 (8.44; 9.14), $p < 0.001$
Pe, %	31.12 (30.34; 31.89)	17.96 (17.30; 18.62), $p < 0.001$	24.14 (23.60; 24.68), $p < 0.001$
Sph, %	24.10 (23.64; 24.49)	43.22 (42.41; 44.05), $p < 0.001$	32.90 (32.0; 33.80), $p < 0.001$
12-HETE, ng/ml	1.81 (1.74; 1.89)	4.84 (4.78; 4.91), $p < 0.001$	3.69 (3.63; 3.74), $p < 0.001$
15-HETE, ng/ml	1.68 (1.63; 1.73)	3.84 (3.75; 3.93), $p < 0.001$	3.17 (3.07; 3.27), $p < 0.001$
Arachidonic acid, %	3.83 (3.77; 3.90)	5.77 (5.69; 5.85), $p < 0.001$	4.38 (4.29; 4.47), $p < 0.001$

Note. p – significance of the differences between subgroups within the main group and the control group.

responses. Sph, as a component of HDL, contributes indirectly to these functions [24].

It should be noted that Sph and its precursor, ceramide, have been implicated in the mechanisms of programmed cell death (apoptosis) under various pathophysiological conditions, including those associated with COVID-19. Studies by international researchers have demonstrated a clear correlation between increased Sph levels and the risk of mortality among patients infected with the SARS-CoV-2 virus. Apoptosis, a process that occurs early on, may contribute to the initiation of lung damage, leading to loss of pulmonary function and respiratory failure [25].

Consequently, phospholipid levels were dependent on the severity of COVID-19. The concentrations of Pc and Pe decreased significantly with increasing severity of the pathological process, whereas Lpc and Sph levels increased significantly depending on the severity of COVID-19.

Oxylipins, which are products of arachidonic acid lipoxygenase metabolism, have been shown to play a significant role in regulating inflammation and oxidative stress. This is achieved through both direct and indirect effects on cells and tissues, including modulation of vascular tone (vasoconstriction and vasodilation) and immune function [26].

As our observations indicate, when analyzing the levels of oxylipins in the blood serum of pregnant women infected with COVID-19 during the second trimester, there are changes in lipid metabolism, as presented in Table 1.

Based on the results of the study, the median concentration of 12-HETE increased by 2.7-fold ($p < 0.001$) in pregnant women in subgroup 1, and by 2-fold ($p < 0.001$) in subgroup 2, compared with the control group (Table 1). The same trend was observed for 15-HETE, with median values increasing by 2.3-fold ($p < 0.001$), and 1.9-fold ($p < 0.001$), respectively, in subgroups 1 and 2 compared to control values (Table 1). These findings suggest increased activity of 12- and 15-lipoxygenase enzymes, as well as activation of lipid peroxidation and oxidative stress in these subgroups.

An increase in the levels of 12-HETE and 15-HETE was observed against the background of high concentrations of arachidonic acid. The median value of arachidonic acid in subgroup 1 increased by 1.51-fold ($p < 0.001$), and in subgroup 2 it increased by 1.14-fold ($p < 0.001$) (Table 1).

The obtained data indicate that exposure to SARS-CoV-2 has significantly increased the concentrations of arachidonic acid metabolites (oxylipins), specifically 12-HETE and 15-HETE, in the blood serum of pregnant women with COVID-19. This increase was most pronounced in cases of moderate disease severity, which may indicate increased activity of 12- and 15-lipoxygenase enzymes, activation of lipid peroxidation pathways, and the development of oxidative stress. Our findings are consistent with those of international researchers, who have also reported elevated levels of 12-HETE in the blood plasma of COVID-19 patients [27]. 12-HETE is known to play a role

in various physiological and pathobiological processes, acting as a chemotactic agent for neutrophils and smooth muscle cells and as a mitogen for endothelial cells [28, 29]. In addition, it has been shown to induce the expression of endothelial cell adhesion molecules, tissue factor on monocytes, and TNF- α in macrophages [29].

In general, HETEs are known for their pro-inflammatory and pro-apoptotic properties [30], suggesting their direct involvement in the development of inflammation in pregnant women with COVID-19. However, recent research has identified some HETEs as anti-inflammatory mediators. For example, 15-HETE, which was found to be elevated in the COVID-19 group compared to healthy controls, is a PPAR γ ligand that can reduce inflammation by inhibiting nuclear factor- κ B and modulating macrophage activity towards an anti-inflammatory phenotype. Additionally, 15-HETE serves as a precursor for lipoxin A4. Lipoxins, in contrast to classical pro-inflammatory arachidonic acid derivatives, exhibit potent anti-inflammatory and resolution-promoting properties. Additionally, 15-HETE undergoes further oxidation to 15-oxo-eicosatetraenoic acid, a class of oxylipins with anti-inflammatory activity [30]. Therefore, our data indicate the simultaneous production of both pro-inflammatory and anti-inflammatory oxylipins, and/or a shift in the temporal expression of lipid mediators towards an anti-inflammatory response, as part of a process known as lipid class switching [31].

Therefore, the findings have allowed us to identify certain trends in changes in the levels of arachidonic acid and its products of lipoxygenase metabolism, oxylipins (12-HETE and 15-HETE), which are key mediators in the pathophysiology of various intra- and intercellular processes, including inflammation associated with COVID-19.

CONCLUSION

The study suggests that the development of COVID-19 during the second trimester of pregnancy is associated with alterations in the levels of phospholipids, arachidonic acid, and oxylipins in the peripheral blood serum. These changes may be related to the severity of the disease process. The identified abnormalities in phospholipid and oxylipin metabolism in pregnant women with COVID-19 could potentially reflect the intensity of the inflammatory response in the respiratory system and could guide the optimization of therapeutic strategies for this patient group.

Funding

The research was funded by the federal budget as part of the state-funded research project of the Federal Research Institute (registration number AAAA-A18-118020790064-4).

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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Information about the authors

Natalia A. Ishutina – Dr. Sc. (Biol.), Professor of FEB RAS, leading staff scientist of the Laboratory of mechanisms of etiopathogenesis and recovery processes of the respiratory system at non-specific lung diseases, Far Eastern Scientific Center of Physiology and Pathology of Respiration; e-mail: ishutina-na@mail.ru, <https://orcid.org/0000-0002-1024-1532>

Irina A. Andrievskaya – Dr. Sc. (Biol.), Professor of the RAS, Head of the Laboratory of mechanisms of etiopathogenesis and recovery processes of the respiratory system at non-specific lung diseases, Far Eastern Scientific Center of Physiology and Pathology of Respiration; e-mail: irina-andrievskaja@rambler.ru, <https://orcid.org/0000-0003-0212-0201>