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ALPHA-1-ANTITRYPSIN – A BIOMARKER OF ANTIPROTEASE PROTECTION IN THE PREDICTION OF PREMATURE BIRTH IN COVID-19 AND HEALTHY PREGNANT WOMEN

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Spontaneous preterm birth is the leading cause of perinatal morbidity and mortality worldwide. This problem has become especially relevant in the COVID-19 era. The purpose of the study was to investigate the association between serum alpha-1-antitrypsin levels and premature birth in COVID-19 and healthy pregnant women. Our study showed that serum alpha-1-antitrypsin levels increase during normal pregnancy. We found that changes in alpha-1-antitrypsin concentrations are an important factor in preterm birth. Namely, there is an inverse relationship between alpha-1 antitrypsin levels and preterm birth: the lower the serum alpha-1 antitrypsin level, the higher the risk of preterm birth. In this study, we found that non-pregnant women with COVID-19 had a lower of alpha-1-antitrypsin levels then healthy non-pregnant women. In group pregnant women with COVID-19 with preterm birth level of α1-AT was approximately 1.5-fold lower in pregnant women with COVID-19 with timely delivery.

Key words: alpha-1-antitrypsin, preterm birth, COVID-19.

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АЛЬФА-1-АНТИТРИПСИН – БІОМАРКЕР АНТИПРОТЕАЗНОГО ЗАХИСТУ У ПРОГНОЗІ ПЕРЕДЧАСНИХ ПОЛОГІВ У COVID-19 ТА ЗДОРОВИХ ВАГІТНИХ

Спонтанні передчасні пологи є основною причиною перинатальної захворюваності та смертності в усьому світі. Ця проблема особливо актуальна в епоху COVID-19. Метою дослідження було дослідити зв'язок між рівнем альфа-1-антитрипсину в сироватці крові та передчасними пологами при COVID-19 та здорових вагітних жінок. Наше дослідження показало, що рівень альфа-1-антитрипсину в сироватці підвищується під час нормальної вагітності. Ми виявили, що зміни концентрації альфа-1-антитрипсину є важливим фактором передчасних пологів. А саме, існує зворотна залежність між рівнем альфа-1 антитрипсину та передчасними пологами: чим нижчий рівень альфа-1 антитрипсину в сироватці крові, тим вищий ризик передчасних пологів. У цьому дослідженні ми виявили, що невагітні жінки з COVID-19 мали нижчий рівень альфа-1-антитрипсину, ніж здорові невагітні жінки. У групі вагітних з COVID-19 із передчасними пологами рівень альфа-1-антитрипсину був приблизно в 1,5 рази нижчим ніж у вагітних із COVID-19 із своєчасними пологами.

Ключові слова: альфа-1-антитрипсин, передчасні пологи, COVID-19.

The study is a fragment of the research project "Development of new highly economical methods of biomarker diagnostics and prediction of the course and complications of COVID-19 and community-acquired pneumonia in military personnel and civilians", state registration number 0123U101246.

Alfa-1-antitrypsin (α1-AT) is a member of the of serum protease inhibitors or family of serpins which also includes α-1-antichymotrypsin, α-2-antiplasmin, plasminogen activator I, thyroxine-binding globulin, cortisol-binding globulin, angiotensinogen and the inhibitor of leukocytes [5]. .Neutrophil elastase, cathepsin G and proteinase constitute the largest inhibitor of α-1-AT in the lung [14]. The lung parenchyma is exposed to the action of these proteolytic enzymes due to the passage of neutrophils through the lung connective tissue. Neutrophilic elastase is released in large quantities amounts in response to neutrophil activation and has as substrates certain components of extracellular matrix. Excessive release of neutrophil elastase results in destruction of the lung parenchyma. Therefore, α1-AT has as an important function to prevent this destruction. Acts as an antienzyme in the lung. α-1-antitrypsin is present in plasma and enters the lungs by passive diffusion. Thelium is relatively permeable to protein, with the concentration in the interstitium being approximately 80% of plasma concentration [7]. Conversely, the epithelium constitutes a relatively impermeable barrier to the movement of the molecule. As it is believed that the destruction of elastin in the lung in the interstitial space is related to the development of emphysema, the concentration of α-1-antitrypsin in the interstitium is critical for protecting lung integrity and is generally similar to that in plasma [4]. α1-AT is the third most abundant protein in plasma and the most prevalent serpin in the body. As an acute phase protein, α1-AT levels increase three- to five-fold with systemic infection or inflammation, underscoring its important homeostatic function [4, 14].

α1-AT deficiency-associated lung disease. There is burgeoning evidence that alpha-1-antitrypsin, the most abundant endogenous serine protease inhibitor (serpin), inhibits SARS-CoV-2 infection and mitigates many of the pathogenic mechanisms of COVID-19 [2, 12, 13]. Even in the absence of frank α1-AT deficiency, the α1-AT response to a systemic infection may be inadequate as has been shown for hospitalized COVID-19 patients [1, 2].

Spontaneous preterm birth is the leading cause of perinatal morbidity and mortality worldwide and continues to present a major clinical dilemma [6, 8, 10]. D'Silva A.M. et al. reported that α1-AT was dysregulated in maternal serum collected at 11–13+6 weeks' gestation from pregnancies that continued to labour spontaneously and deliver preterm [6].

The purpose of the study was to investigate the association between serum alpha-1-antitrypsin levels and premature birth in COVID-19 and healthy pregnant women.

Materials and methods. The studies were carried out on the basis of city and regional hospitals in 2015–2022. In accordance with the provisions of the Declaration of Helsinki by the World Medical Association of the last revision (1964-2013) and informed consent for the use of biological material was obtained in all patients prior to inclusion in the study. Research permission was obtained from the Bioethics Committee of the Lugansk State Medical University (Rubizhne, Ukraine, number 25/2015). The patients' epidemiological data, laboratory examination, complications, clinical outcomes, CT imaging data, and treatment plan were extracted from medical records. The date of onset of the disease was the date of the first symptom.

All cases of SARS-CoV-2 infection confirmed by a positive result on real-time reverse transcriptase polymerase chain reaction tests of a nasal sample and/or diagnosed by a computed tomography chest scan were included and analyzed [10].

To test our hypothesis, this case-control study consisted of:

– 14 healthy non-pregnant female donors aged 18 to 42 years (control group);

– 53 pregnant women aged 17 to 46 years in terms of pregnancy from 8 to 41 weeks in the absence of signs of preeclampsia and placental insufficiency, whose pregnancy ended with the birth of live children at gestational age:

– 26–36 weeks – 25 pregnant women,

– 40 weeks and> – 28 pregnant women

– 16 pregnant women with COVID-19 – childbirth at 36-41 gestation;

– 17 women with a positive diagnosis of COVID-19 according to PCR analysis (9 pregnant women with COVID-19-timely delivery; 7 pregnant women with COVID-19-preterm birth);

The material for the study was the peripheral blood from the cubital vein of patients and healthy donors. 10 ml of blood was collected in vacuum tubes (BD Vacutainer, heparin-sodium). The blood tubes were inverted 5-6 times to mix the blood with the anticoagulant and placed on ice. Then the blood was centrifuged at 2000 g at 4°C for 15 minutes. on a refrigerated centrifuge K-24 (Germany). The serum was aliquoted and transferred to cryogenic tubes for storage at -40°C prior to the study. Before testing, all samples underwent one freeze-thaw cycle.

Alpha-1-antitrypsin levels in serum were determined by the immunoturbidimetric method using an automatic biochemical analyzer Mindray BS 120. Blood glucose was measured by the Rayto RT-1904C analyzer (Rayto Life and Analytical Sciences), using the glucose oxidase method (GLUCOSE PAP AD727GP).

Data Processing. Statistical and graphical analyses were done using STATISTICA 7.0 (StatSoft Inc. USA, version 7.0) and and MedCalc Version 20.218 64 bit (MedCalc Software, Ostend, Belgium). Parametric data were summarized as mean (standard error) (Mean±SEM). Kolmogorov–Smirnov test was applied to examine the normality of data distribution. To examine group-wise differences, unpaired Student's t-test was used. Receiver operating characteristics (ROC) curve analysis was performed to estimate optimal cut-off values, maximizing sensitivity and specificity according to the Youden index. Survival analysis (the advent of severe acute respiratory syndrome within 30 days of hospitalization) was performed using the Kaplan–Meier method; univariate analys were undertaken using log rank test and Cox's regression model, respectively. A p-value below 0.05 was considered statistically significant. The Cox proportional hazards regression model was used to assess the effect of serum alpha-1-antitrypsin levels on clinical outcomes in survival analysis.

Results of the study and their discussion. During the study, we divided pregnant women into two groups: healthy pregnant women and pregnant women with COVID-19. We have set the level of alpha-1-antitrypsin in pregnant women (with and without COVID-19) (Table 1).

Healthy pregnant women with timely delivery (40-41 weeks of gestation) showed higher values of alpha-1-antitrypsin (3.78±0.03 g/l) in comparison with healthy non-pregnant women (2.69±0.05 g/l; p=0.0000001). Serum levels of α1-AT was reduced in healthy women who laboured spontaneously and delivered preterm. Namely, healthy pregnant women with preterm birth (26-36 weeks of gestation) had a lower mean alpha-1-antitrypsin concentration in their serum than did the pregnant women with timely delivery (2.03±0.03 g/l) and (3.78±0.03 g/l; p=0.0000001) respectively.

Table 1

Level of alpha-1-antitrypsin in COVID-19 and healthy pregnant women

Groups	Valid N	Mean, g/l	SEM	p-value
healthy non-pregnant women	14	2.69	0.05	p=0.0000001$^{\&}$ p=0.027881$^{\&\&}$
healthy pregnant women-timely delivery (40-41 weeks of gestation)$^{@}$	28	3.78	0.03	p=0.0000001* p=0.0000001$^{\&}$ p=0.0000001$^{\&\&}$
healthy pregnant women-preterm birth (26-36 weeks of gestation)$^{@}$	25	2.03	0.03	p=0.0000001* p=0.0000001** p=0.0000001$^{\&}$ p=0.0000001$^{\&\&}$
COVID-19-non-pregnant women	17	1.35	0.03	p=0.0000001*
pregnant women with COVID-19-timely delivery (40-41 weeks of gestation)$^{@}$	9	2.9	0.08	p=0.027881* p=0.0000001$^{\&}$
pregnant women with COVID-19-preterm birth (26-36 weeks of gestation)$^{@}$	7	1.9	0.03	p=0.0000001* p=0.0000001** p=0.0000001$^{\&}$ p=0.0000001$^{\&\&}$

Notes: $^{@}$ – The samples were collected within 24 hours before delivery. Data are means ± SEM for Gaussian variables Intergroup by the T-test Students * – p – significant differences between control (healthy non-pregnant women) and all test groups (women) ** – p – significant differences between pregnant women-preterm birth and test groups of pregnant women-timely delivery (with and without COVID-19) $^{\&}$ – p – significant differences between COVID-19-non-pregnant women and other test groups $^{\&\&}$ – p – significant differences between pregnant women with COVID-19-timely delivery and all test groups

Non-pregnant women with COVID-19 had a lower of alpha-1-antitrypsin levels then healthy non-pregnant women (1.35±0.03 g/l and 2.69±0.05 g/l; respectively, p=0.0000001). In group pregnant women with COVID-19 with preterm birth (26-36 weeks of gestation) level of α1-AT was approximately 1.5-fold lower in pregnant women with COVID-19 with timely delivery (40-41 weeks of gestation) (1.9±0.03 g/l and 2.9±0.08 g/l; respectively, p=0.0000001). At the same time, the level of α1-AT in this group was significantly lower in pregnant women with COVID-19 than in healthy pregnant women.

Analysis of the ROC curve in healthy pregnant women and pregnant women with COVID-19 is shown in Fig. 1.

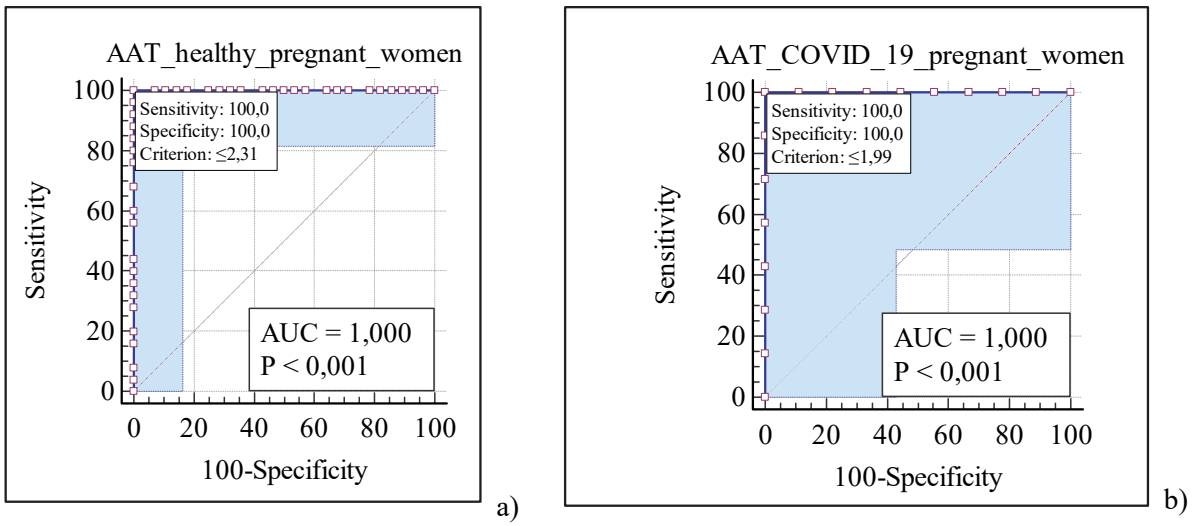


Fig. 1. ROC analysis: receiver operating characteristic (ROC) curves for alpha-1-antitrypsin measured in a) healthy pregnant women; b) pregnant women with COVID-19. Note: Here and in the following figures: p<0.001 – calculated by univariate logistic regression analysis.

The optimal cut-off for alpha-1-antitrypsin values identified by ROC analysis were as follows: healthy pregnant women with preterm birth, 2.31 g/l; pregnant women with COVID-19 with preterm birth, 1.99 g/l. The results of ROC analysis with determination of the area under the operating characteristics

curve (AUC - Area Under Curve) for the α1-AT index as a predictor of preterm birth, as well as the corresponding sensitivity and specificity values for the optimal cut-off points are presented in Table. 2.

Table 2

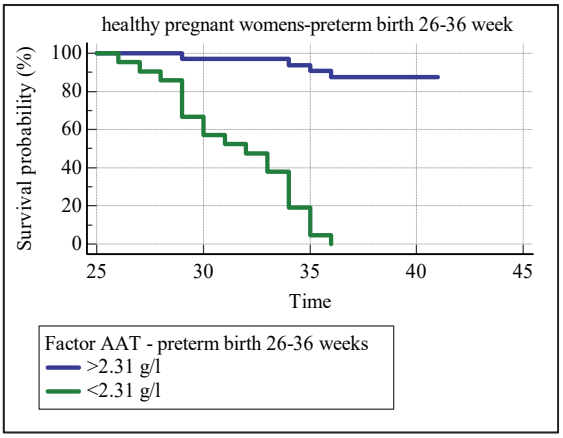
The sensitivities, specificities and the cut-off value of alpha-1-antitrypsin in COVID-19 and healthy pregnant women with preterm birth 26-36 week of gestation

Groups	cut-off value	Area, AUC	Sensi-tivity	95% CI	Speci-ficity	95% CI	p-value
alpha-1-antitrypsin –healthy pregnant women – preterm birth 26-36 week of gestation	≤2.31	1.000	100.0	86.3 – 100.	100.0	87. – 100.0	<0.0001
alpha-1-antitrypsin –COVID-19 pregnant women – preterm birth 26-36 week of gestation	≤1.99	1.000	100.0	59.0 – 100.0	100.0	66.4 – 100.0	<0.0001

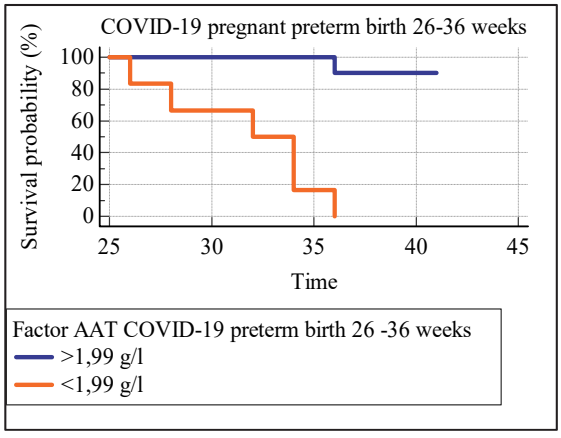
Note: p-value was calculated by univariate logistic regression analysis of the area under the curve (AUC) in the group.

The values of area under the curve (AUC) was 1.000 with a sensitivity of 100.0 % (95% CI 86.3 – 100.0) and specificity of 100.0 % (95 % CI 87.7 – 100.0) for the α1-AT in healthy pregnant women with preterm birth 26-36 week of gestation, which reflects the high predictive effectiveness of this index for preterm birth. In pregnant women with COVID-19, the AUC was also 1.000, indicating good diagnostic accuracy. When assessing the diagnostic indicator, it was found that the optimal threshold value, that is, the α1-AT cutoff point, is 1.9 g/l. A decrease of more than 1.9 g/l predicts the risk of preterm with a sensitivity of 100.0 % (95 % CI 59.0 – 100.0) and specificity of 100.0 % (95 % CI 66.4 – 100.0).

Kaplan-Meier survival curves after classifying patients based on Youden's cutoff values obtained using ROC curves showed a higher risk of preterm birth depending on the α1-AT levels (Fig. 2): healthy pregnant women with preterm birth 26-36 week of gestation (HR = 36.93; 95 % CI 14.05 – 97.12, p<0.0001); pregnant women with COVID-19 with preterm birth 26-36 week of gestation (HR = 46.72; 95 % CI 7.42 – 294.1, p<0.0001).



a)



b)

Fig. 2. Kaplan–Meier curves of preterm birth 26-36 week of gestation of a) healthy pregnant women; b) pregnant women with COVID-19 with different cut-off values of the of indexes investigated. p value by Long-rank test. Note: Here and in the following figures: p<0.0001 – calculated by univariate logistic regression analysis.

Next, we performed a Cox proportional hazards regression analyses of predictors for preterm birth 26-36 week of gestation in healthy pregnant women and pregnant women with COVID-19 are presented in Fig. 3.

In univariate analysis, the α1-AT ≤2.31 g/l.(p<0.0001) was significantly associated with an increased risk of preterm birth in healthy pregnant women with preterm birth 26-36 week of gestation (HR = 0.07; 95 % CI 0.02 – 0.24, p<0.0001); and in pregnant women with COVID-19 with preterm birth 26-36 week of gestation – with an α1-AT ≤1.9 g/l.(p<0.0001) (HR = 0.0072; 95 % CI 0.0001 – 0.876, p=0.044).

HR – odds ratio, represents the increased or decreased risk of achieving the end point (premature birth) at any point in time associated with a unit increase in the corresponding parameter, taking into account the predictor effect. If HR >1 means an increased chance of an unfavorable outcome (that is, the factor has a direct connection with the onset of premature birth). If H <1 - reduced chance of achieving the end point during the study (that is, the factor is protective and has an inverse relationship with the likelihood of an unfavorable outcome).

Since our Cox regression analysis showed an HR<1, there is an inverse relationship between alpha-1-antitrypsin levels and preterm birth, namely, the lower the serum alpha-1-antitrypsin level, the higher the risk of preterm birth.

Harrell's C-index, also known as the concordance index, is a goodness of fit measure for models which produce risk scores. All parameters that were significant at a p value less than 0.10 could predict the preterm birth 26-36 week of gestation in healthy pregnant women (C-index=0.849, 95 % CI 0.78 – 0.92, p<0.0001), pregnant women with COVID-19 (C-index=0.890, 95 % CI 0.822 – 0.958) increases the risk of a poor prognosis of the preterm birth at 26-36 week of gestation.

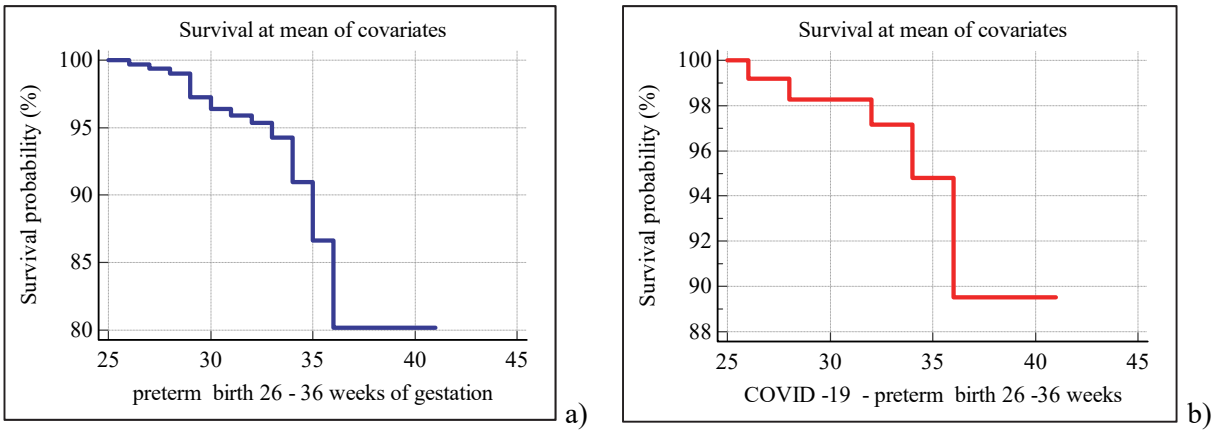


Fig. 3. Cox proportional hazard regression analyses of predictors for preterm birth 26-36 week of gestation: a) healthy pregnant women; b) pregnant women with COVID-19. Note: Here and in the following figures: p<0.0001 – calculated by univariate logistic regression analysis.

Thus, as a result of stepwise logistic regression analysis, a model was selected with an independent predictor that increases the risk of preterm birth, the significance level of which did not reach 0.050, which included the alpha-1-antitrypsin factor, which retained statistical significance as part of the multivariate Cox regression model of the proportional risk of an unfavorable outcome.

Our study, as well as other investigators, showed that serum alpha-1-antitrypsin levels increase during normal pregnancy. This has potential clinical significance because alpha-1-antitrypsin promotes endometrial angiogenesis and vascularization and inhibits the activity of cathepsins, tissue plasminogen activator and kallikrein, participating in trophoblast invasion and implantation [3]. But pregnancy-associated increases in alpha-1-antitrypsin levels in women with severe alpha-1 antitrypsin deficiency do not reach levels considered normal [9].

We found that changes in alpha-1-antitrypsin concentrations are an important factor in preterm birth. Namely, there is an inverse relationship between alpha-1 antitrypsin levels and preterm birth: the lower the serum alpha-1 antitrypsin level, the higher the risk of preterm birth.

Alpha-1-antitrypsin has been shown to protect the lungs from acute lung injury. Since an imbalance of protease and anti-protease is implicated in the pathogenesis of COVID-19 acute lung injury, absolute or relative deficiency of functional alpha-1-antitrypsin is a plausible risk factor for severe COVID-19 [2]. Hospitalized patients with severe COVID-19 had significantly lower plasma α1-AT levels than those admitted for non-COVID-19 pneumonia [15]. The concept of “relative alpha-1-antitrypsin deficiency” is known, where factors such as oxidative stress, high glucose, and bacterial proteases inactivate normal alpha-1-antitrypsin [2]. Our previous study identified alpha-1-antitrypsin as a prognostic marker for poor prognosis in COVID-19 in the setting of hyperglycemia. Levels of α1-AT in COVID-19 patients with hyperglycemia who survived > those who did not survive [11].

French researchers have shown high rates of premature birth in patients with COVID-19. Thus, the rate of premature births up to 37 weeks was 65 %, and up to 32 weeks – 40 % [10]. It is no coincidence that we were interested in searching for a biomarker and predictor of preterm birth in pregnant women with COVID-19.

In this study, we found that non-pregnant women with COVID-19 had a lower of alpha-1-antitrypsin levels then healthy non-pregnant women. In group pregnant women with COVID-19 with preterm birth (26-36 weeks of gestation) level of α1-AT was approximately 1.5-fold lower in pregnant women with COVID-19 with timely delivery (40-41 weeks of gestation).

Alpha-1 antitrypsin expression in the amnion, which is the inner layer of the fetal membrane lining the amniotic cavity, is regulated by cytokines (such as tumor necrotic factor alpha, interleukin-6 and

oncostatin M). α1-AT inhibits production of pro-inflammatory cytokines [2]. In amnion from pregnancy with premature rupture of the membrane, α1-AT activity was significantly lower [9]. These findings were accompanied by elevated levels of circulating proinflammatory cytokines. Thus, the deficiency of alpha-1-antitrypsin as a protective factor against tissue damage from enzymes secreted by inflammatory cells, which are involved in both premature birth and COVID-19, is pathogenetically significant.

Conclusions

1. The deficiency of alpha-1-antitrypsin was significantly associated with an increased risk of preterm birth in healthy pregnant women with preterm birth 26-36 week of gestation.

2. COVID-19 creates a deficiency of alpha-1-antitrypsin in pregnant women, which is increased during normal pregnancy.

3. Our results from pregnant women with COVID-19 showed that lower serum α1-AT levels are a prognostic factor for preterm birth.

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