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V.M. Komarevtsev, K.V. Balabanova[1] , Yu.A. Chernykh[2],
I.E. Karasev, I.S. Haydash, I.A. Haydash, I.O. Komarevtseva
State Establishment "Lugansk State Medical University", Rivne
[1]Center for nursing development of the MOH of Ukraine, Kyiv
[2]National Cancer Institute, Kyiv

ALFA-1-ANTITRYPSIN IS A PROGNOSTIC RISK OF DEVELOPING PREGNANCY-ASSOCIATED KIDNEY AND UTERINE DISEASES

e-mail: kialdmu@ukr.net

The purpose of the study was to investigate the role of the biomarker of alpha-1-antitrypsinin the the development of pregnancy-associated renal cell carcinoma and pregnancy-associated uterine sarcoma within 1 years (56 weeks) and 35 years after childbirth. Our data proved the diagnostic value of determining the alpha-1-antitrypsin level for detecting cancer diseases, both in pregnant and non-pregnant women. Oncological diseases significantly increase the level of alpha-1-antitrypsin compared to all groups of healthy women. This is especially true for healthy pregnant women with preterm labor, where the increase in alpha-1-antitrypsin level in pathologies is 2.69 times. Using variation series of alpha-1-antitrypsin levels in blood serum of pregnant women with different periods of pregnancy, we created a prognostic risk model for the development of pregnancy-related cancer during the first year and during 35 years after preterm and timely birth, depending on the level of alpha-antitrypsin.

Key words: alpha-1-antitrypsinin, pregnancy-associated renal cell carcinoma, pregnancy-associated uterine sarcoma.

В.М. Комаревцев, К.В. Балабанова, Ю.А. Черних, І.Е. Карасев, І.С. Гайдаш, І.А. Гайдаш, І.О. Комаревцева

АЛЬФА-1-АНТИТРИПСИН – ПРОГНОСТИЧНИЙ ПОКАЗНИК РИЗИКУ РОЗВИТКУ ВАГІТНІСТЬ-АСОЦІЙОВАНИХ ЗАХВОРЮВАНЬ НИРКИ ТА МАТКИ

Метою дослідження було вивчення ролі ролі біомаркеру альфа-1-антитрипсину у розвитку асоційованого з вагітністб нирково-клітинного раку та пов'язаної з вагітністю саркоми матки протягом 1 року (56 тижнів) після пологів та на термін до 35 років. Наші дані доказали діагностичну цінність визначення рівня альфа-1-індитрипсину для виявлення захворювань раку, як у вагітних, так і у жінок, що не мають вагітності. Онкологічні захворювання значно збільшують рівень альфа-1-антитрипсину порівняно з усіма групами здорових жінок. Особливо це стосується здорових вагітних жінок з передчасними пологами, де підвищення рівня альфа-1-антирипсину в патологіях становить 2,69 рази. Використовуючи варіаційні рядки рівня альфа-1-антитрипсину в сироватці крові вагітних жінок з різними періодами вагітності, ми створили модель прогностичного ризику для розвитку раку пов'язаного з вагітністю протягом першого року та протягом 35 років після передчасного та своєчасного народження залежно від рівня альфа-антитрипсину.

Ключові слова: альфа-1-антирипсин, вагітність-асоційований рак нирки, вагітність-асоційована саркома матки.

The study is a fragment of the research project "Development and implementation of innovative technologies for the diagnosis of oncogynecological and oncourological diseases based on liquid biopsy data of extracellular DNA and stem cells", state registration No. 0123U101248.

Cancer in pregnancy is defined as any cancer that occurs during pregnancy or in the first postpartum year. It is the second leading cause of mortality in women of reproductive age. Cancer complicates an estimated 1 in 1000 pregnancies [10, 12, 13].

Gynecologic malignancies, along with breast and hematologic malignancies, are of the most common cancers diagnosed in pregnancy. Uterine leiomyoma are the most common gynecologic tumor in reproductive aged women and are found in 10–20 % of pregnancies [10]. A meta-analysis demonstrated an increased risk of kidney cancer in parous compared with nulliparous women, and an increase in risk with each subsequent birth [5].

Prompt diagnosis is mandatory in the management of these conditions and multidisciplinary care is important, involving both gynecologists and gynecological oncologists, along with radiation oncologists, in order to choose the best treatment approach [12].

Tumor markers are biochemical substances found in the presence of cancer and produced either by the tumor itself or in response to (para)neoplastic conditions, such as inflammation. Tumor markers can be found in a variety of bodily fluids and tissues and include hormones and several subgroups of (glyco)proteins, such as oncofetal antigens (which are normally expressed during fetal life), enzymes and receptors. They are used for diagnosis, assessment of therapeutic efficacy, and detecting recurrence during follow-up. The most limiting factor in the clinical use of tumor markers is the lack of sensitivity and specificity because the majority of markers are tumor-associated rather than tumor-specific; elevated levels can occur in different types of malignancies as well as in benign and physiological conditions such as pregnancy [7].

The purpose of the study was to investigate the role of the biomarker of alpha-1-antitrypsinin the the development of pregnancy-associated renal cell carcinoma and pregnancy-associated uterine sarcoma within 1 years (56 weeks) after childbirth.

Materials and methods. The studies were carried out on the basis of city and regional hospitals of the Luhansk region between 2009 to 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 (Luhansk, Ukraine, number 12/2009, Rubizhne, 25/2015, Rivne, 1/26.09.2022). The patients' epidemiological data, laboratory examination, complications, clinical outcomes, CT imaging data, and treatment plan were extracted from medical records. The main end point of this study was the diagnostic time of pregnancy-compiled cancer in the first year after childbirth and 5-year survival at other cancers.

To test our hypothesis, this case-control study consisted of the indicators of alpha-1-antitrypsinin (AAT) in the blood serum of 16 patients with pregnancy-associated renal cell carcinoma (PA-RCC); 38 patients with renal cell carcinoma (RCC); 8 patients with pregnancy-associated uterine sarcoma (PA-US) and 11 patients with uterine sarcoma (US). The clinical diagnosis in all patients was confirmed by morphological examination of the tumor according to the classification of kidney tumors of the World Health Organization (WHO/ISUP) [2]. According to the TNM classification, patients with malignant kidney tumors had stages of the tumor process: pregnancy-associated renal cell carcinoma $T_1N_0M_0$ – 4 (25 %), $T_2N_0M_0$ – 9 (56 %), $T_3N_0M_0$ – 3 (19 %); renal cell carcinoma $T_1N_0M_0$ – 8 (21 %), $T_2N_0M_0$ – 25 (66 %), $T_3N_0M_0$ – 4 (10 %), $T_4N_2M_0$ – 1 (3 %). According to the WHO International Classification of Diseases for Oncology, third edition (ICD-O-3) morphology codes [8]; histological subtypes of uterine sarcoma were defined as follows:

– Carcinosarcoma: Mullerian mixed tumor (n=0), Mesodermal mixed tumor (n=2),

– Carcinosarcoma, not otherwise specified (NOS) (n=3).

– Leiomyosarcoma: Leiomyosarcoma, NOS (n=4), Epithelioid leiomyosarcoma (n=2), Myxoid leiomyosarcoma (n=0).

– Stromal sarcoma: Endometrial stromal sarcoma (n=3), Endometrial stromal sarcoma, low-grade (n=0), Stromal sarcoma, NOS (n=0).

– Adenosarcoma (n=2).

– Sarcoma, NOS (n=3).

We determined the extent of disease at diagnosis using the International Federation of Gynecology and Obstetrics (FIGO) staging system:

– FIGO stage I (n=5, 63 % patients with pregnancy-associated uterine sarcoma and n=4, 36 % patients with uterine sarcoma) – localized stage, when the tumor is limited to the uterus;

– FIGO stages II (n=3, 37 % patients with pregnancy-associated uterine sarcoma and n=5. 46 % patients with uterine sarcoma) and III (0 patients with pregnancy-associated uterine sarcoma and n=2, 18 % patients with uterine sarcoma) – regional stage, when the tumor has spread to nearby tissues or lymph nodes;

– FIGO stages IVA and IVB (n=0 patients) – distant stage, if the tumor has spread further.

Tumor grade was defined as follows: grade I, well differentiated; grade II, moderately differentiated; grade III, poorly differentiated; and grade IV, undifferentiated, anaplastic.

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). 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 was 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 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.

Results of the study and their discussion. During the study, we divided women into groups: healthy non-pregnant women and pregnant women, women with pregnancy-associated renal cell carcinoma, renal cell carcinoma, pregnancy-associated uterine sarcoma and uterine sarcoma, in which we studied the level of circulating alpha-1-antitrypsin in the blood serum (Table 1).

Table 1

Level of Alpha-1-antitrypsin (g/L)

Groups	n	Alpha-1-antitrypsin, g/l	p level
healthy non-pregnant women	14	2.69±0.05	
healthy pregnant women-timely delivery	28	3.78±0.03	p^1=0.0000001
healthy pregnant women-preterm birth	25	2.03±0.03	p^2=0.0000001
pregnancy-associated renal cell carcinoma	16	5.19±0.1	p^1=0.0000001 p^2=0.0000001 p^3=0.0000001
renal cell carcinoma	38	4.76±0.07	p^1=0.0000001 p^2=0.0000001 p^3=0.0000001
pregnancy-associated uterine sarcoma	8	5.46±0.08	p^1=0.0000001 p^2=0.0000001 p^3=0.0000001
uterine sarcoma	11	5.19±0.11	p^1=0.0000001 p^2=0.0000001 p^3=0.0000001
Urollitiasis	38	3.86±0.03	p^1=0.0000001 p^2=0.097276 p^3=0.0000001

Note: Data are means ± SEM for Gaussian variables.

Intergroup by the T-test Students: p^1 – significant differences between group healthy non-pregnant women with test other groups, p^2 – significant differences between group healthy pregnant women-timely delivery with test other groups, p^3 – significant differences between group healthy pregnant women-preterm birth with test other groups.

The level of alpha-1-antitrypsin in the serum of women with pregnancy-associated renal cell carcinoma (5.19±0.1 g/l) is 1.93-fold higher than in healthy non-pregnant women (2.69±0.05 g/l, p=0.0000001); 1.37-fold higher than in healthy pregnant women with timely delivery (3.78±0.03 g/l, p=0.0000001); and 2.56-fold higher than in healthy pregnant women with preterm delivery (2.03±0.03 g/l, p=0.0000001). The level of alpha-1-antitrypsin in the serum of women with pregnancy-associated uterine sarcoma (5.46 ± 0.08 g/l) is 2.03-fold higher than in healthy non-pregnant women (2.69±0.05 g/l, p=0.0000001); 1.44-fold higher than in healthy pregnant women with timely delivery (3.78 ± 0.03 g/l, p=0.0000001); and 2.69-fold higher than in healthy pregnant women with preterm delivery (2.03±0.03 g/l, p=0.0000001). The level of alpha-1-antitrypsin in the serum of women with renal cell carcinoma (4.76±0.07 g/l) is 1.77-fold higher than in healthy non-pregnant women (2.69±0.05 g/l, p=0.0000001); 1.26-fold higher than in healthy pregnant women with timely delivery (3.78±0.03 g/l, p=0.0000001); and 2.34-fold higher than in healthy pregnant women with preterm delivery (2.0 ± 0.03 g/l, p=0.0000001). The level of alpha-1-antitrypsin in the serum of women with uterine sarcoma (5.19±0.11 g/l) is 1.93-fold higher than in healthy non-pregnant women (2.69±0.05 g/l, p=0.0000001); 1.37-fold higher than in healthy pregnant women with timely delivery (3.78±0.03 g/l, p=0.0000001); and 2.56-fold higher than in healthy pregnant women with preterm delivery (2.03±0.03 g/l, p=0.0000001). In women of patients with urolithiasis, the level of alpha-1-antitrypsin (3.86±0.03 g/l) was in 1.43-fold higher than in healthy non-pregnant women (2.69±0.05 g/l, p=0.0000001); in 1.02-fold higher (statistically insignificant) than in healthy pregnant women with timely delivery (3.78±0.03 g/l, p=0.097276); and 1.9-fold higher than in healthy pregnant women with preterm delivery (2.03±0.03 g/l, p=0.0000001).

This visualization clearly demonstrates the differences between the groups and can be used for differential diagnosis (Fig. 1).

Further, using the variation rows of alpha-1-antitrypsin levels in the blood serum of pregnant women with various pregnancy periods, we have created a prognostic risk model for the development of pregnancy-assholed cancer in the first year after premature and timely birth depending on the alpha-1-antitrypsin level.

The prognostic model (Fig. 2) was made using Python with several key libraries:

1. **NumPy** (`numpy`) – for mathematical calculations and array operations
2. **Pandas** (`pandas`) – for creating and working with data tables
3. **Matplotlib** (`matplotlib.pyplot`) – for data visualization

4. **SciPy** (`scipy.stats`) – for statistical calculations

Specifically, the forecast is built on a mathematical model of exponential decay.

Fig. 1. Correlation Analysis.

Prognosis dynamics were:

– For the group with timely delivery, a gradual decrease in indicators to normal values is expected within a year.

– For the group with preterm delivery, a slow increase in indicators is predicted.

– By the end of the year (after 12 months), the indicators of both groups are expected to converge to normal value.

Next, we developed a prognostic model for assessing the risk of developing uterine sarcoma in women during the 35-year period after childbirth based on changes in alpha-1-antitrypsin levels (Fig. 3)

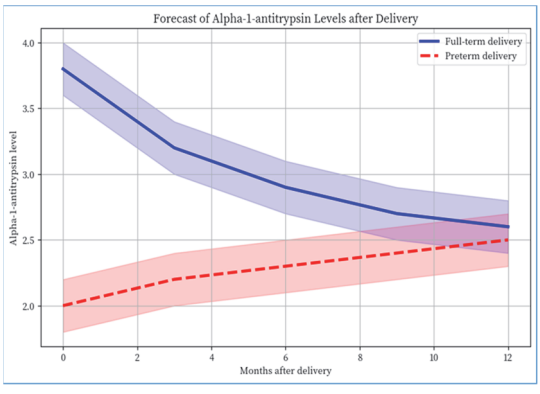

Fig. 2. The prognostic model of changing alpha-1-antitrypsin levels in women within a year after childbirth at the time of 26–36 weeks and 40–41 weeks.

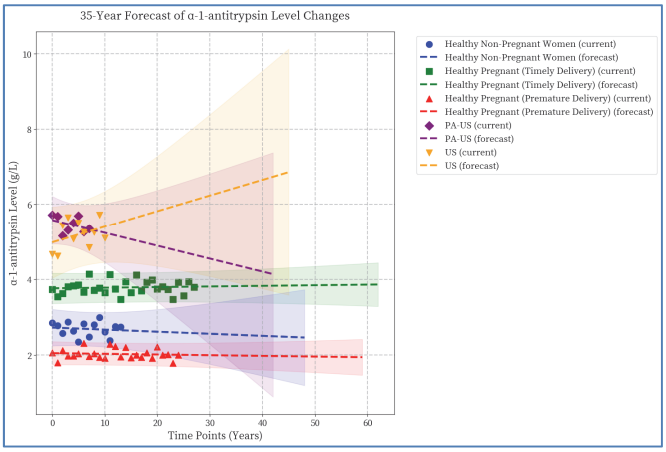

Fig. 3. The prognostic model for assessing the risk of developing uterine sarcoma in women during the 35-year period after childbirth based on changes in alpha-1-antitrypsin levels.

Main trends the prognostic model for assessing the risk of developing uterine sarcoma in women:

– The most stable indicators are expected in healthy pregnant women with timely delivery (change of only +2.1 %).

– Significant changes are predicted for PA-US (decrease of 24.2 %) and US (increase of 32.2 %).

– Healthy non-pregnant women and pregnant women with premature delivery are expected to show moderate decreases in indicators.

– The widest confidence intervals are observed for PA-US and US, indicating greater uncertainty in forecasts for these methods.

Next, we developed a prognostic model for assessing the risk of developing renal cell carcinoma in women during the 35-year period after childbirth based on changes in alpha-1-antitrypsin levels (Fig. 4).

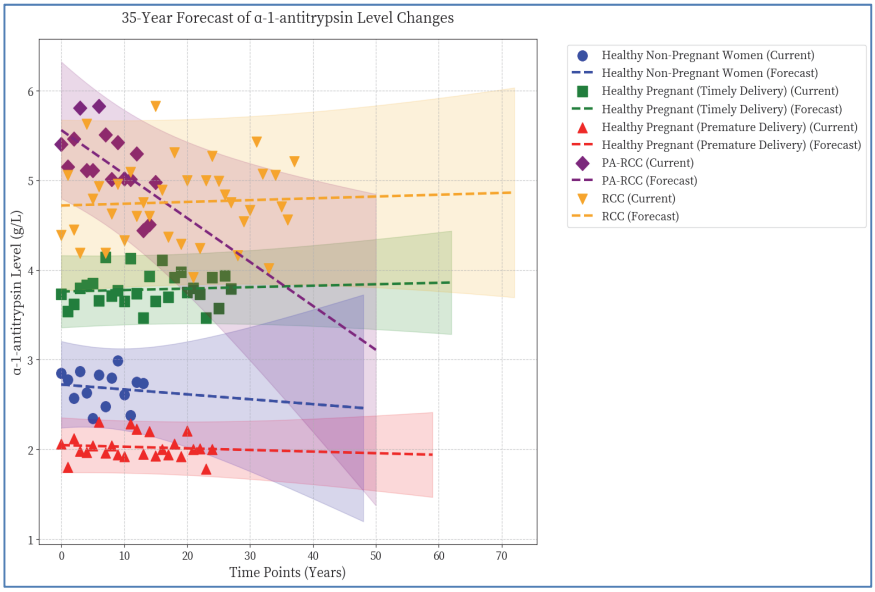

Fig. 4. The prognostic model for assessing the risk of developing renal cell carcinoma in women during the 35-year period after childbirth based on changes in alpha-1-antitrypsin levels.

Key changes of the prognostic model for assessing the risk of developing renal cell carcinoma in women:

– The PA-RCC group shows the most dramatic decrease (40.1 %).

– Groups of healthy non-pregnant women and pregnant women with premature delivery show moderate decreases.

– RCC and healthy pregnant women with timely delivery groups show slight increases.

The extended forecast period has led to more pronounced change trends.

There is evidence indicating a role for AAT in pregnancy [3, 6, 9]. Indeed, AAT has been suggested as important to angiogenesis and vascularisation of the endometrium, as well as trophoblast invasion and embryo implantation. Associations between low AAT levels and pregnancy-related complications, such as preeclampsia, spontaneous abortion, and preterm labour, have also been described [3, 4, 6, 9]. Nevertheless, evidence is still limited regarding the clinical consequences of a Deficiency (AATD) on pregnancy, and less so regarding the use of AAT therapy in pregnant women [4, 6].

Feng Y, et al. (2016) found that AAT levels were significantly decreased in placenta tissues from women with preeclampsia compared that of healthy wome [3]. As our studies have shown the greatest differences of the alpha-1-antitrypsin levels are observed when comparing with the group of healthy pregnant women with preterm delivery, where the increase in AAT levels in pathologies reaches 2.69-fold. Pregnancy with oncological diseases leads to an even greater increase in AAT levels compared to non-pregnant patients with the same diseases. The liteature has shown that AAT play a significant role in regulating cell-to-cell and cell-to-matrix interactions, releasing growth factors and cytokines that can promote cell proliferation and invasion [1, 14, 15]. AAT is a protease inhibitor that protects tissues from the inflammatory cells proteases. Furthermore, high AAT levels have also been described in association with tumors bladder cancer, colorectal cancer, cervical cancer and lung cancer [11], suggesting its involvement in tumor development. We believe thatthe high level of AAT is explained by the suppression of apoptosis with renal cell carcinoma and uterine sarcoma, but the specific mechanism of action of AAT requires further investigation.

Conclusions

1. Our data confirm the diagnostic value of determining alpha-1-antitrypsin levels for detecting oncological diseases in both pregnant and non-pregnant women.

2. Oncological diseases significantly increase the level of alpha-1-antitrypsin compared to all groups of healthy women.

Diagnostic significance of alpha-1-antitripsin:

– indicators > 5.0 g/l is characteristic of oncological processes;

– values of 3.5–4.5 g/l can indicate urolithiasis;

– values <3.0 g/l are typical for healthy individuals.

3. Particular attention should be paid to the differences between normal and pathological pregnancy.

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