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BIOMARKER SIGNIFICANCE OF CIRCULATING DNA ACCORDING TO LIQUID BIOPSY IN PATIENTS WITH PREGNANCY-ASSOCIATED CANCER AND UROGENICOLOGICAL CANCER

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The purpose of the study was to investigate the role of the biomarker of circulating cell-free DNA in the the development of pregnancy-associated renal cell carcinoma and pregnancy-associated uterine sarcoma within 1 years (56 weeks) after childbirth. To test our hypothesis, this case-control study consisted of the indicators of cfDNA in the blood serum of 16 patients with pregnancy-associated renal cell carcinoma; 38 patients with renal cell carcinoma; 8 patients with pregnancy-associated uterine sarcoma and 11 patients with uterine sarcoma. We have established a high level of circulating cell-free DNA in sick women, both renal cell carcinoma and uterine sarcoma, as well as the pregnancy-associated renal cell carcinoma and pregnancy-associated uterine sarcoma, at all stages of the tumor process. in our study, The mathematical prognostic model of changing circulating cell-free DNA levels in women during the year after childbirth within 26–36 weeks and 40–41 weeks, confirmed a high and moderate risk of developing pregnancy-associated cancer in the first 12–24 weeks after childbirth, which corresponds to the time diagnostics of the pregnancy-associated cancer in our study. The pathogenetic platform of the development of pregnancy-associated cancer is a high level of circulating cell-free DNA in women during pregnancy and the first 12–24 weeks after birth in a period of 40–41 weeks and especially with premature birth in 26–36 weeks

Key words: circulating cell-free DNA, pregnancy-associated renal cell carcinoma, pregnancy-associated uterine sarcoma.

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БІОМАРКЕРНА ЗНАЧУЩІСТЬ ЦИРКУЛЮЮЧОЇ ДНК ЗА ДАНИМИ РІДИННОЇ БІОПСІЇ У ХВОРИХ НА ВАГІТНІСТЬ-АСОЦІЙОВАНИЙ РАК І УРОГІНЕКОЛОГІЧНИЙ РАК

Метою дослідження було дослідити роль біомаркера циркулюючої безклітинної ДНК у розвитку раку нирок, пов'язаного з вагітністю, та саркомі матки, пов'язаної з вагітністю, протягом 1 року (56 тижнів) після пологів. Щоб перевірити нашу гіпотезу, це дослідження контроль-випадок, складалося з показників циркулюючої фрагментованої ДНК у сироватці крові 16 пацієнтів із вагітність-асоційованим раком нирки; 38 пацієнтів з раком нирки; 8 пацієнтів із саркомою матки, пов'язаної з вагітністю, та 11 пацієнтів із саркомою матки. Ми встановили високий рівень циркулюючої фрагментованої ДНК у жінок хворих, як на вагітність-асоційований рак нирки і вагітність-асоційовану саркому матки, так і на нирко-клітинні рак та саркому матки неасоційовану з вагітністю на всіх стадіях пухлинного процесу. Математична прогностична модель зміни рівнів циркулюючої фрагментованої ДНК у жінок протягом року після пологів протягом 26–36 тижнів та 40–41 тижнів підтвердила високий та помірний ризик розвитку раку, пов'язаного з вагітністю, протягом перших 12–24 тижнів після пологів, що відповідає діагностиці раку, пов'язаного з вагітністю у нашому дослідженні. Патогенетична платформа розвитку раку, пов'язаного з вагітністю, ґрунтується на високому рівню циркулюючої фрагментованої ДНК у жінок під час вагітності та у перші 12–24 тижнів після пологів у термін 40–41 тижнів і особливо з передчасними пологами у 26–36 тижнів.

Ключові слова: фрагментована ДНК, 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.

In recent years, the influence of pregnancy on subsequent maternal health has become an important focus of research. Changes in reproductive patterns (*i.e.,* having fewer children and giving birth at older ages), pregnancy complications, and exposures occurring earlier in life are being examined, the connection of hormones, pregnancy and other reproductive factors is studied with the subsequent risk of cancer in the mother [10].

Much of what is known about the epidemiology of uterine cancer relates to endometrial cancer, as uterine sarcomas comprise only 3–7 % of uterine malignancies [6].

The relations between pregnancy characteristics and other malignancies have been much less investigated than breast, endometrial, and ovarian cancers. This is likely due to the less pronounced hormonal etiology of these malignancies and their lower incidence [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 [3].

During normal pregnancy, tumor markers including CA 15.3, squamous cell carcinoma antigen and CA 125 can be elevated; inhibin B, anti-Müllerian hormone and lactate dehydrogenase levels remain below normal cut-off values. Knowledge of physiological variations during pregnancy can be clinically important when managing gynecological cancers in pregnant patients [4].

Interest in the use of cell-free nucleic acids (cfNAs) as clinical non-invasive biomarker panels for prediction and prevention of multiple diseases has greatly increased over the last decade. Indeed, circulating cfNAs are attributable to many physiological and pathological processes such as imbalanced stress conditions, physical activities, extensive apoptosis of different origin, systemic hypoxic-ischemic events and tumour progression [1]. More recently, in some European countries, a non-invasive pregnancy test (NIPT) has been introduced – this is a screening test of bloodless fetal DNA in blood samples to detect potential anomalies in early pregnancy. For example, it has been offered in the Netherlands to all pregnant women since April 2023 [8].

When comparing the circulating cell-free DNA (cfDNA) level in serum healthy pregnant women and pregnant women with premature births, we have established a high level of its premature births and proved the cfDNA biomarker role in physiological and pathological pregnancy [9].

The purpose of the study was to investigate the role of the biomarker of circulating cell-free DNA in 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 cfDNA in the blood serum of 16 patients with pregnancy-associated renal cell carcinoma (PARCC); 38 patients with renal cell carcinoma (RCC); 8 patients with pregnancy-associated uterine sarcoma (PAUS) 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 [6, 7]; 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.

DNA fragmentation in blood serum was measured with the diphenylamine assay as reported previously [9]. The material for the study was the peripheral blood from the cubital vein of pregnant women. 10 ml of blood was collected in vacuum tubes (BD Vacutainer PLUS). 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 to separate serum on a refrigerated centrifuge K-24 (Germany). Serum was aliquoted and transferred to cryogenic tubes for storage at –40 °C prior to the study. A 1 ml sample from serum eluate is taken from the homogenate. The amount of fragmented DNA (f-DNA) was calculated in percentage as the ratio of the amount of extracted DNA (in the supernatant) to the total amount of DNA in the sample.

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. Receiver operating characteristics (ROC) curve analysis was performed to estimate optimal cut-off values, maximizing sensitivity and specificity according to the Youden index. The appearance of metastases analysis was performed using the Kaplan–Meier method; univariate and multivariate analyses 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 cfDNA levels on the the diagnostic time of pregnancy-compiled cancer in the first year after childbirth in survival analysis.

Results of the study and their discussion. During the study, we divided women into groups: healthy 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 cfDNA in the blood serum (Table 1).

Table 1

Level of cfDNA in women with cancer

Groups	n	cfDNA. %	p level
healthy women	14	24.2±0.82	
pregnancy-associated renal cell carcinoma	16	86.9±1.45	p^1=0.0000001
renal cell carcinoma	38	75.2±1.0	p^1=0.0000001 p^2=0.0000001
pregnancy-associated uterine sarcoma	8	92.9±1.73	p^1=0.0000001
uterine sarcoma	11	76.3±2.33	p^1=0.0000001 p^2=0.000057

Note: Data are means ± SEM for Gaussian variables. Intergroup by the T-test Students, p^1 – significant differences between group healthy womens with test other groups, p^2 – significant differences between groups of pregnancy-associated cancer and test other groups of cancer.

Comparison of the level of cfDNA in serum of healthy women and women with cancer of all studied groups showed a high level of cfDNA in women with women with cancer patients: healthy women – 24.2±0.82 %; women with pregnancy-associated renal cell carcinoma – 86.9±1.45 %; women with renal cell carcinoma – 75.2±1.0 %; women with pregnancy-associated uterine sarcoma – 92.9±1.73 %; women with uterine sarcoma – 76.3±2.33 %; p=0.0000001.

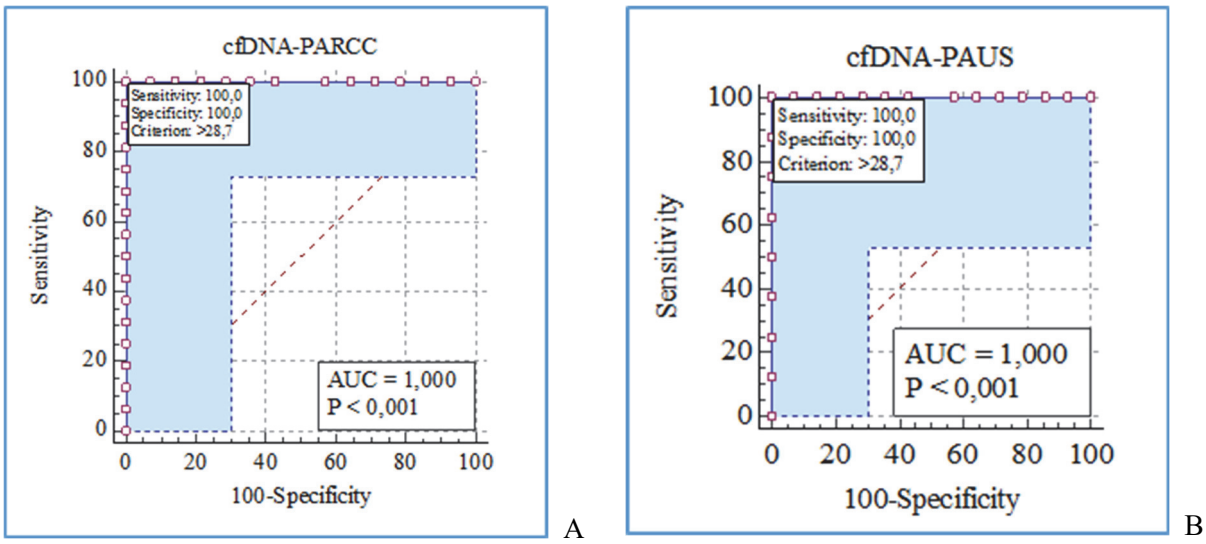
Women with pregnancy-associated renal cell carcinoma and pregnancy-associated uterine sarcoma the level of cfDNA in serum was higher than women with renal cell carcinoma and uterine sarcoma.

Analysis of the ROC curve in patients with pregnancy-associated renal cell carcinoma and pregnancy-associated uterine sarcoma is shown in Fig. 1.

ROC analysis was based on the cfDNA indicator. According to the curve of the receiver's work characteristics, the area under the ROC (AUC) cfDNA curve for predicting the development of pregnancy-associated renal cell carcinoma is 1.000 (p<0.001) with a sensitivity of 100.0 % (95% CI 79.4 – 100.0) and specificity of 100.0 % (95 % CI 76.8 – 100.0), optimal cut-off values of cfDNA – >28.7 %; pregnancy-associated uterine sarcoma AUC=1.000 (p<0.001) with a sensitivity of 100.0 % (95 % CI 63.1 – 100.0) and specificity of 100.0 % (95 % CI 76.8 – 100.0), optimal cut-off values of cfDNA – >28.7 %.

The Kaplan–Meier survival curves (Fig.2), after classifying the patients on the basis of Youden cut-offs obtained by ROC curves, showed a higher risk and time of development PARCC within 1 years (56 weeks) after childbirth, the Mean of which was 47.6±2.08 weeks (95 % CI for the mean 43.5 to 51.7).

The hazard ratio (HR) was (HR = 0.022; 95 % CI 0.0017 to 0.28, p = 0.0031). Thus, the optimal cut-off values of cfDNA – < 28.7 % reduces the risk of the development of pregnancy-associated renal cell carcinoma by 97.8 % (100 × (1 − HR) %).

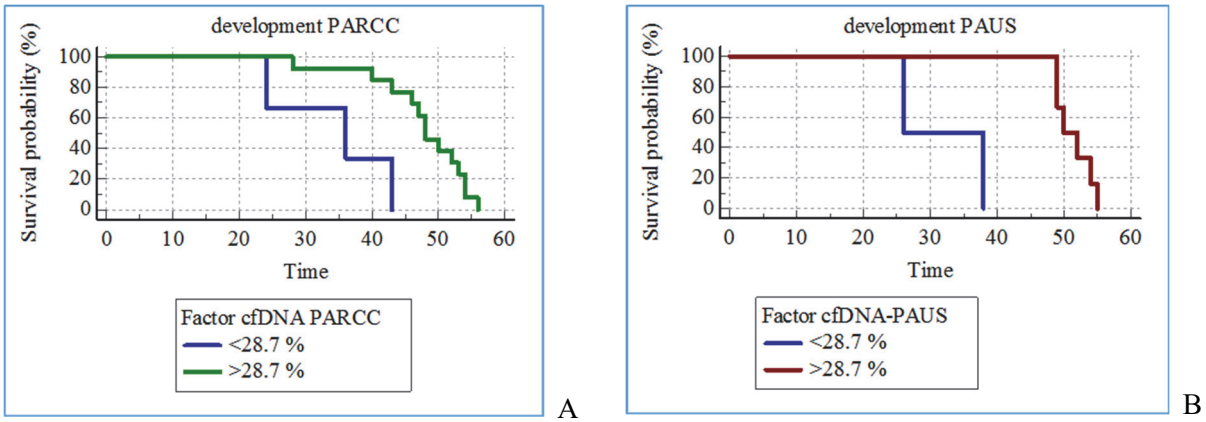


A B

Fig. 1. ROC analysis: receiver operating characteristic (ROC) curves for cfDNA measured in patients with: A – pregnancy-associated renal cell carcinoma; B – pregnancy-associated uterine sarcoma.

Note: Here and in the following figures: p<0.001 – calculated by univariate logistic regression analysis.

A higher risk and time of development PAUS within 1 years (56 weeks) after childbirthwas also observed, the Mean of which was 51.5±1.06 weeks (95 % CI for the mean 49.4 to 53.6), The hazard ratio (HR) was (HR = 0.0056; 95 % CI 0.0002 to 0.19, p = 0.0031). Thus, the optimal cut-off values of cfDNA – < 28.7 % reduces the risk of the development of pregnancy-associated uterine sarcoma by 94.4 % (100 × (1 − HR) %).



A B

Fig. 2. Kaplan–Meier curves of the time of development PARCC (A) and PAUS (B) within 1 years (56 weeks) after childbirth with different cut-off values 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 (Fig.3) of predictors for the time of development PARCC and PAUS within 1 years (56 weeks) after childbirth. In univariate analysis, cfDNA was significantly associated with an increased risk of development PARCC and PAUS within 1 years (56 weeks) after childbirth. in observation groups.

In Cox regression (as in logistic regression), the null hypothesis (the predictor has no relationship with the dependent variable, i.e. its regression coefficient is not significantly different from zero) is tested using the Wald criterion. If the regression coefficient is significantly different from zero, then the independent variable makes a significant contribution to the predictive ability of the model, which is what our results show. Coefficient Exp(B), which shows how many times the risk of an outcome occurring changes if the value of the predictor changes by one. If the value of Exp(B) or the risk ratio is greater than one, then the positive value of this factor will be a factor associated with the risk of developing the outcome, if less than one, then it will be associated with an increase in survival time (that is, it will act as a protective factor with respect to the outcome). The Cox model shows that cfDNA (both in the group of the PACRR and in the PAUS group) acts as a protective factor that prevents tumor development, since Exp(b) (Hazard

Ratio) < 1 and is equal to PACRR group – 0.78 (p=0.0009); PAUS group – 0.81 (p=0.0026); Harrell's C-index PACRR group =0.812, PAUS group=0.798 as values close to 1, which indicate high performance of the Cox-model.

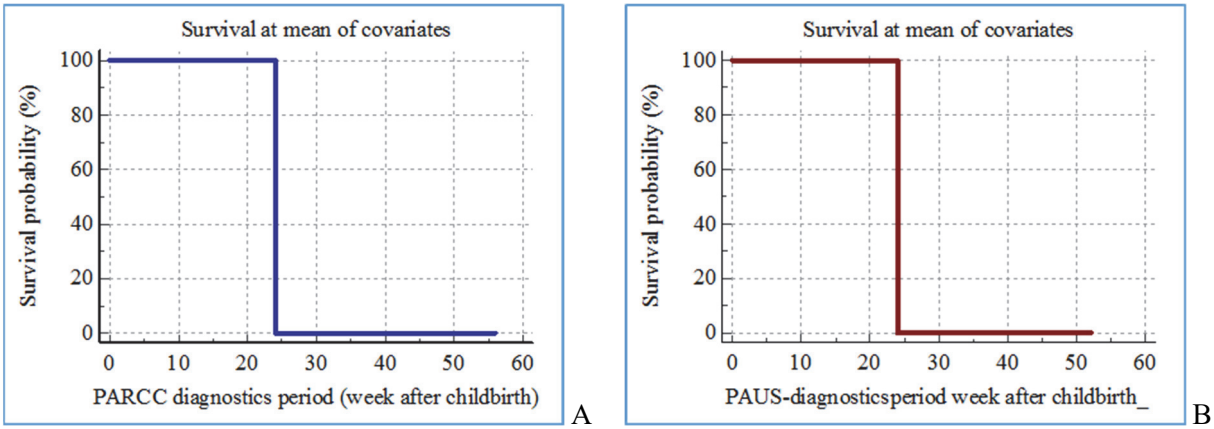


Fig. 3. A Cox proportional hazards regression analyses of predictors for the time of development PARCC (A) and PAUS (B) within 1 year (56 weeks) after childbirth.

Further, using the variation rows of cfDNA 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 cfDNA level (Table 2).

Table 2

The level of cfDNA, %

cfDNA level in pregnant women during premature birth in 26–36 weeks of gestation				cfDNA level in pregnant women with timely birth in 40–41 weeks of gestation				
8–10 weeks	14–16 weeks	20–24 weeks	26–36 weeks	8–10 weeks	14–16 weeks	20–24 weeks	26–28 weeks	40–41 weeks
33.78	52.07	62.43	71.33	45.73	45.73	53.72	80.88	60.88
34.36	52.06	56.45	72.57	40.56	40.56	47.15	82.05	62.05
33.54	63.05	54.3	72.88	39.95	39.95	51.56	79.36	57.36
39.13	58.07	58.57	65.67	40.72	40.72	47.59	81.68	61.68
37.72	64.55	56.7	70.02	42.64	42.64	52.05	80.53	60.53
44.69	48.45	67.31	68.08	33.61	33.61	53.42	79.8	49.8
40.45	62.72	61.21	72.52	46.19	46.19	54.21	85.91	65.91
35.88	52.69	55.52	65.39	44.46	44.46	49.11	85.55	65.55
36.94	54.14	55.46	70.85	38.16	38.16	48.05	84.56	64.56
38.6	56.68	65	70.2	38.8	38.8	57.19	82.23	62.23
30.23	54.76	56.71	67.96	38.15	38.15	54.79	81.94	61.94
41.51	57.24	61.21	66.02	34.19	54.52	59.43	85.12	65.12
35.5	51.48	51.19	67.84	33.91	56.37	56.26	84.12	64.12
31.65	43.09	55.41	74.29	45.78	54.39	54.23	81.76	61.76
31.29	58.24	56.87	74.55	33.78	55.61	55.72	79.47	59.47
25.38	47.67	58.2	69.02	37.13	55.56	51.75	83.66	63.66
38.05	53.75	61.15	68.25	37.01	50.2	47.43	84.17	64.17
43.13	58.25	62.46	72.35	44.2	53.96	56.41	84.93	48.93
27.03	44.38	60.19	65.69	39.65	53.25	51.87	85.16	65.16
31.98	49.17	57.97	74.91	45.76	52.95	53.53	79.24	59.24
25.09	53.64	56.4	72.88	38.48	51.03	54.55	81.86	61.86
36.69	56.9	52.6	73.15	36.18	57.66	49.96	82.62	62.62
18.92	65.07	57.03	71.1	45.98	64.56	47.7	82.85	62.85
39.18	55.29	59.07	65.05	35.12	54.15	49.23	80.75	60.75
25.11	48.83	55.79	72.46	45.18	52.5	53.09	84.94	64.94
				39.97	52.94	57.29	84.89	55.89
				32.05	55.14	59.86	81.3	61.3
				40.24	59.14	54.2	79.48	59.48

The prognostic model (Fig. 4) was made using Python with several key libraries: – `pandas` – for data manipulation:

– `numpy` – for mathematical calculations

– `matplotlib` – for creating plots

– `scipy.optimize` – for optimization and curve fitting

Key forecast components:

– Used exponential decay function:

```python
def exp_decay(x, a, b, c):
return a * np.exp(-b * x) + c.
```

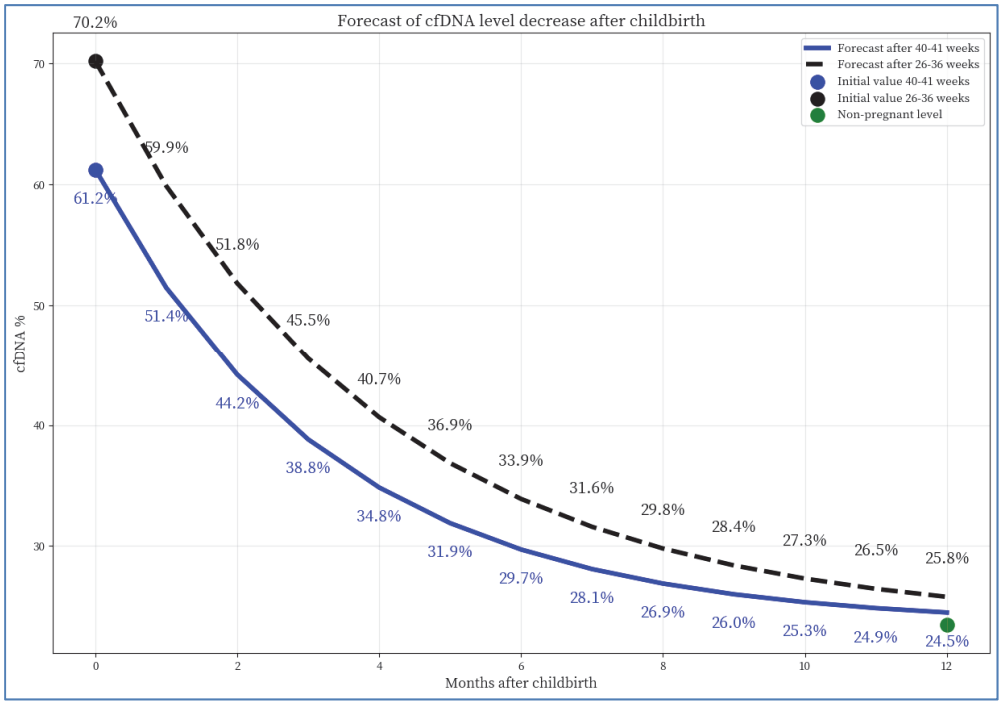


Fig. 4. The prognostic model of changing cfDNA levels in women within a year after childbirth at a period of 26–36 weeks and 40–41 weeks.

Model parameters:

– For 40–41 weeks: initial value cfDNA= 61.23 %, decay coefficient = 0.3;

– For 26–36 weeks: initial value cfDNA= 70.20 %, decay coefficient = 0.25;

– Base level (non-pregnant) cfDNA = 23.47 %.

Based on the analysis of the data provided and the constructed prognostic model, the following conclusions can be drawn:

Forecast of reduction:

– a gradual decrease in the level of cfDNA during the year is expected;

– the achievement of the basic level (23.47 %) is predicted about 20–24 weeks after birth.

Risk zones:

– high risk: first 12 weeks after childbirth;

– moderate risk: 12–24 weeks;

– low risk: after 24 weeks (subject to normalization of indicators).

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 [4]. In our previous study, we found that the optimal cut-off of the cfDNA level is highly sensitive and highly specific when identifying gestation and childbirth during physiological pregnancy, as well as the forecast of premature birth and the outcome of pregnancy during pathology [9].

In this study, we have established a high level of cfDNA in sick women, both renal cell carcinoma and uterine sarcoma, as well as the pregnancy-associated renal cell carcinoma and pregnancy-associated uterine sarcoma, at all stages of the tumor process. Similar results were obtained by other researchers [5, 11].

Before the implementation of the NIPT in the Netherlands, a large study was carried out (Trident-2) to collect information about the connection of the circulating cell-free DNA in the samples of the mother's blood with malignant neoplasms. Authors found that 16 out of 65 (24.6 %) had a NIPT result malignant suspicious and 49 (75.4 %) women had a normal NIPT result [8]. In contrast to this study, in our study, we established the optimal cut-off values of cfDNA – < 28.7 % reduces the risk of the development of pregnancy-associated renal cell carcinoma by 97.8 % and the development of pregnancy-associated uterine sarcoma by 94.4 %.

The mathematical prognostic model of changing cfDNA levels in women during the year after childbirth within 26–36 weeks and 40–41 weeks, confirmed a high and moderate risk of developing pregnancy-associated cancer in the first 12–24 weeks after childbirth, which corresponds to the time diagnostics of the pregnancy-associated cancer in our study.

Conclusions

1. Our study demonstrates the diagnostic and prognostic potential of serum cfDNA as a biomarker for pregnancy-associated renal cell carcinoma, renal cell carcinoma, pregnancy-associated uterine sarcoma and uterine sarcoma.

2. The pathogenetic platform of the development of pregnancy-associated cancer is a high level of cfDNA in women during pregnancy and the first 12–24 weeks after birth in a period of 40–41 weeks and especially with premature birth in 26–36 weeks.

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