Electronic Journal of General Medicine
2023, 20(3), em473
e-ISSN: 2516-3507
https://www.ejgm.co.uk/

MODESTUM

Original Article

OPEN ACCESS

The model of screening for preeclampsia in the second and third trimesters of gestation

Liudmyla Berlinska [1]*, Valerie Marichereda [1], Oleksandr Rohachevskyi [2], Alla Volyanska [1], Ganna Lavrynenko [1]

[1] Department of Obstetrics and Gynecology, Odesa National Medical University, Odesa, UKRAINE
[2] Department of Simulation Medical Technologies, Odessa National Medical University, Odesa, UKRAINE
***Corresponding Author:** ludaberlinskaja@gmail.com

Citation: Berlinska L, Marichereda V, Rohachevskyi O, Volyanska A, . The model of screening for preeclampsia in the second and third trimesters of gestation. Electron J Gen Med. 2023;20(3):em473. https://doi.org/10.29333/ejgm/12992

ARTICLE INFO

Received: 12 Nov. 2022

Accepted: 13 Feb. 2023

ABSTRACT

Purpose: Preeclampsia (PE) is a specific syndrome of multiple organ insufficiency in case of pregnancy, which is included in the panel of major obstetric syndromes and is among the main causes of maternal morbidity and mortality in the whole world.

Material and methods: We conducted a prospective cohort study of 91 pregnant women to evaluate the effectiveness of integrated use of maternal risk factors (2019 International Federation of Gynecology and Obstetrics recommendations), placenta location (ultrasound at 18-20 weeks of gestation), and serum cystatin C (at 18-36 weeks of gestation) in screening for pe in the second and third trimesters of gestation.

Results: In the subgroup of pregnant women with cystatin C levels greater than 1.0 mg/L (27 women), PE developed in 26 women, which is 96.29% in percentage terms. When calculating GFR for cystatin C in a group with PE there was a significant violation of the renal filtration system -52.46±2.08 (95% CI, 48.39-56.54), while in healthy group the indicator is within normal limits -97.6±1.64 (95% CI, 94.38-100.82). In the analysis of the ratio of cystatin C levels more than 1.0 mg / l and the development of PE, a sensitivity of 98.46%, specificity of 100% and accuracy of 98.9%, $p<0.001$.

Conclusions: The data show that the combined model of maternal factors, ultrasound of the placenta and serum cystatin C, is prognostically effective in pregnant women in the second and third trimesters of gestation and is a reliable marker for the development of pe.

Keywords: preeclampsia, maternal risk factors, cystatin-C

INTRODUCTION

Concept of Preeclampsia

Preeclampsia (PE) is a specific syndrome of multiple organ damage in pregnancy that is among the major obstetric syndromes and is the leading cause of maternal morbidity and mortality worldwide.

Given the numerous positive studies of preventive and therapeutic measures to reduce the complications of PE, the world scientific community offers screening tests to identify risk groups [1-6]. For example, the American College of Obstetricians and Gynecologists (ACOG) [7] and the National Institute for Health and Care Excellence (NICE) have proposed screening for pe based on maternal risk factors. One factor (hypertension in a previous pregnancy, chronic hypertension, chronic kidney disease, diabetes mellitus, autoimmune disease) or more than one moderate factor (first birth, age 40 years or older, family history of pe, pregnancy interval >10 years, body mass index (BMI) 35 kg/m^2 or greater) is considered high risk for PE. From 12 weeks' gestation until birth, it is recommended that high-risk women take 75 to 150 mg of aspirin per day [2].

Risk Factors for Preeclampsia

PE risk factor screening significantly increases the use of low-dose aspirin does not statistically reduce the diagnosis of pe but has a significant reduction effect [8]. However, a combined first-trimester screening test (maternal factors, mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor) as recommended by the Fetal Medicine Foundation (FMF) and approved by the International Federation of Gynecology and Obstetrics (FIGO). Low-dose aspirin of 150 mg/day is prescribed for high-risk women <16 weeks to 36 weeks of pregnancy [5].

Research Problem

Combined FMF screening provides a significant improvement in clinical outcomes compared with the practice of risk factor screening by effectively reducing the frequency of positive results and improving the targeted use of aspirin prophylaxis [9]. However, due to the numerous pathological links in the development of PE, no universal screening currently exists, prompting the scientific community to search

for markers with high specificity and sensitivity, wide availability, noninvasiveness, and low cost. According to FIGO recommendations, all pregnant women should be screened for PE in the first trimester of pregnancy, considering maternal risk factors and BP. The proposed biomarkers are the potential in early diagnosis, but more evidence is needed at this stage [10].

A history of chronic kidney disease and hypertension before or during a previous pregnancy most often leads to acute kidney injury (AKI) preceding the clinical development of PE.

The kidney disease

Improving Global Outcomes (KDIGO) organization held a 2019 discussion conference titled “early detection and intervention in CCN”. During the event, a strategy for screening, risk stratification, and treatment of early CCN was defined. Conclusions regarding the ideal initial screening approach suggested including a panel of “triple markers” of serum creatinine, cystatin C, and urinary albumin to creatinine ratio. It was also agreed with the 2012 KDIGO recommendations to include cystatin C as a critical component of accurate risk stratification, which markedly reinforces the association between GFR and cardiovascular events, renal failure, and death [11].

Research Focus

Recent evidence suggests that cystatin C is a promising biomarker for detecting pe during the third trimester of pregnancy, especially pregnancies complicated by hypertension, or even for predicting high-risk pregnancies [12, 13], which has better predictive value than creatinine in the diagnosis of renal damage, even in the early stages [14-16]. An additional advantage is the determination of FFR by cystatinin C without the requirement to include race quotient, age, sex, and muscle volume as required for creatinine [17]. Creatinine FFR assessment is also unreliable during episodes of AKI [11], whereas PE is a common cause of AKI [18-19]. The main predictor of maternal and fetal outcomes is intra-gestational FFR determination [20, 21] and provides an opportunity to anticipate preterm delivery in patients with severe PE [22]. Thus, we can suggest the feasibility of using cystatin C as a biomarker of early renal damage in PE.

Research Aim and Research Questions

The main factor in the development of PE is impaired placentation. The impact on the development of impaired complete blood supply associated with asymmetry in the blood supply to the right and left halves of the uterus, the presence of low- and nonvascular zones, unequal arterial flow to the anterior and posterior walls of the uterus [23], will result in the incorrect transformation of the maternal uterine spiral arteries broad sinusoids and, consequently, to pe [24]. That is, it is possible to assume the advisability of attention regarding the place of placental attachment using ultrasound examination.

Study objectives

Study objective is to identify the relationship of screening criteria for PE. Objectives of the study can be listed, as follows:

1. To evaluate the effectiveness of the combined use of maternal risk factors, placental location, and serum cystatin C in screening for pe in the second and third trimesters of gestation.
2. Comparison of glomerular filtration rate levels for cystatin C and creatinine among pregnant women examined between the groups with and without pe.
3. To propose a three-component screening model for pe in the first, second, and third trimesters of pregnancy.

RESEARCH METHODOLOGY

General Background

The study was conducted in accordance with international ethical and moral standards. The study is a prospective cohort study. Written consent was concluded with each patient, where she was familiarized with the therapy tactics and gave her consent to participate in the study. The study adhered to the principles of anonymity and confidentiality of the information obtained.

Sample/Participants/Group/Gestational Age Placenta Location/Serum Cystatin C Levels

A prospective cohort study of 91 pregnant women was conducted in 2018-2020 based on the women’s consultation and obstetric hospital of Maternity Hospital No. 2, Odessa. Average age of pregnant women 22.5±2.5 years, 20 to 27 years.

At the first stage of the study, 56 (61.54%) women with factors, according to the 2019 FIGO recommendations, associated with the development of pe were assigned to the main group (group I1); the control group (group I2) consisted of 35 (38.46%) virtually healthy pregnant women. The second stage of allocation per subgroup was based on certain placental locations on ultrasound examination at 18-20 weeks of gestation. 47 (51.65%) pregnant women were assigned to the subgroup with the placenta located along the anterior uterine wall (subgroup II1) and 44 (48.35%) with the placenta located along the posterior uterine wall (subgroup II2). The third stage of allocation was at gestational age 18-36 weeks (mean was 32.22±0.41 weeks), based on serum cystatin C levels (1.0 mg/L). 27 (29.67%) pregnant women had cystatin C 1.0 mg/g (subgroup III1) and 64 (70.33%) pregnant women had 1.0 mg/l (subgroup III2). In a final step, preliminary data were analyzed in the groups of pregnant women with pe (group IV1), 26 (28.57%), and those who had not developed pe (group IV2), 65 (71.43%). PE was determined according to the recommendations of the International Society for the Study of Hypertension in Pregnancy and approved by FIGO [5].

General exclusion criteria were cancer, tuberculosis, severe somatic pathology in decompensation, mental illness, chronic alcoholism, drug addiction, and injuries during pregnancy that resulted in obstetric complications.

Instrument and Procedures

Ultrasound assessment of placental location was performed at 18-20 weeks of gestation using a ToshibaAplio 400 universal expert ultrasound machine (Japan) [9].

Serum cystatin C was studied in women without clinical manifestations of PE in the second or third trimester of gestation (18-36 weeks) and measured by an immunoturbidimetric method using Cystatin C reagent on an ADVIA 1800 device according to the manufacturer’s instructions, manufacturer “Siemens” (USA) [5, 14, 15].

Table 1. Characteristics of the mother: age, height, weight, and BMI before pregnancy*

	I_1 main	95% DI	I_2 control	95% ДІ	p	IV_1 PE	95% DI	IV_2 without PE	95% DI	p
Age	31.88±0.86	30.19-33.56	28.37±0.74	26.92-29.82	0.006*	30.65±1.25	28.21-33.10	30.48±0.72	29.06-31.89	0.899
Height	166.05±0.81	164.46-167.65	166.23±1.74	162.82-169.64	0.919	163.35±1.26	160.87-165.82	167.23±1.02	165.23-169.20	0.034*
Weight	73.69±2.48	68.83-78.54	61.85±1.48	58.96-64.75	0.001*	71.80±3.66	64.63-78.98	68.07±1.93	64.28-71.86	0.332
BMI*	26.70±0.86	25.00-28.39	22.50±0.59	21.35-23.65	0.001*	26.83±1.29	24.31-29.36	24.38±0.68	23.06-25.71	0.071

Note. BMI-Body mass index; p*>0.05; *General sampling characteristics=0.3; &n=91

Data Analysis

We analyzed the data entered in MS Excel using a PC statistical program, version 3.6.2 (Foundation for Statistical Computing, Vienna, Austria). We used descriptive analysis of intergroup comparisons to determine the most important factors in the development of pe, descriptive analysis of intergroup comparisons, and determination of maximum sensitivity and specificity limit levels for serum cystatin C, creatinine, and urea levels. Receiver operating characteristic (ROC) plots were used. Between-group comparisons were performed by one-way ANOVA using the Pearson correlation coefficient. A $p<0.05$ value was considered statistically significant. Given the sample size (91 women), the statistical significance, considering the sample size, is 0.95. Thus, the representativeness of the results obtained is at the level of $p\leq0.05$.

RESULTS

Maternal, Obstetric, and Extragenital Factors of PE.

Among 91 (100%) pregnant women in our study, 26 (28.57%) women developed pe. In our study, the age composition of pregnant women in groups I1 versus I2 was statistically significantly higher, p=0.05, but there was no difference between groups IV1 and IV2 (p=0.05) (**Table 1**).

When analyzing ROC area under the curve (AUC) chart, no significant difference was demonstrated between age and the development of PE (AUC in group IV1 was 0.54, IV2 was 0.46); the model is unsatisfactory. In women aged 35 years or older, a sensitivity of 70.77% and specificity of 30.77%, with an accuracy of 59.34%, an odds ratio of 1.08 (95% CI 0.4 to 2.89) but p>0.05 was observed in relation to PE. The mean age composition of our study was 30.53±0.62 (95% CI 29.3-31.75). It is possible to assume that this led to a low significance of the effect of age on the development of PE.

In our study, there was a statistically significant difference in weight and BMI of women before pregnancy between groups I1 and I2, p<0.001, whereas in the analysis between groups IV1 and IV2 there was no statistical difference in weight and BMI values, (p>0.05) (**Table 1**). In the ROC analysis of pregnant women's AUC BMI relative to PE, an average quality (0.62) was noted for women in group IV1 and an unsatisfactory quality (0.38) in group IV2, suggesting a negligible probability of the effect of increasing BMI on the development of PE. At a BMI ratio >30 kg/m^2, the PE calculated a sensitivity of 84.62% and specificity of 23.08% with an accuracy of 67.03%, the odds ratio was 1.65 (95% CI 0.53 to 5.13), but p>0.05. At a maximum BMI of 36.85 kg/m^2 by PE, the sensitivity was 60%, the specificity 90.91% with an accuracy of 81.25%, the odds ratio 15. Thus, our study observed a high risk of PE in pregnant women starting with second-degree obesity.

There was no statistical risk in the growth analysis between groups I1 and I2, (p>0.05). However, statistically significant results were observed between groups IV1 and IV2 (p=0.034, Cohen's d 0.5 (95% CI: 0.38 to 0.62)) (**Table 1**). Consequently, our study suggests that women with less than average height have an increased risk of developing PE.

Thus, among maternal characteristics, such as age, height, weight, and BMI before pregnancy, the greatest influence on the development of PE was noted in the pregnant woman's short stature and obesity (BMI 36 kg/m^2). The influence of age, weight, and BMI 30 kg/m^2 before pregnancy on the development of PE was not statistically confirmed in our study (**Table 1**).

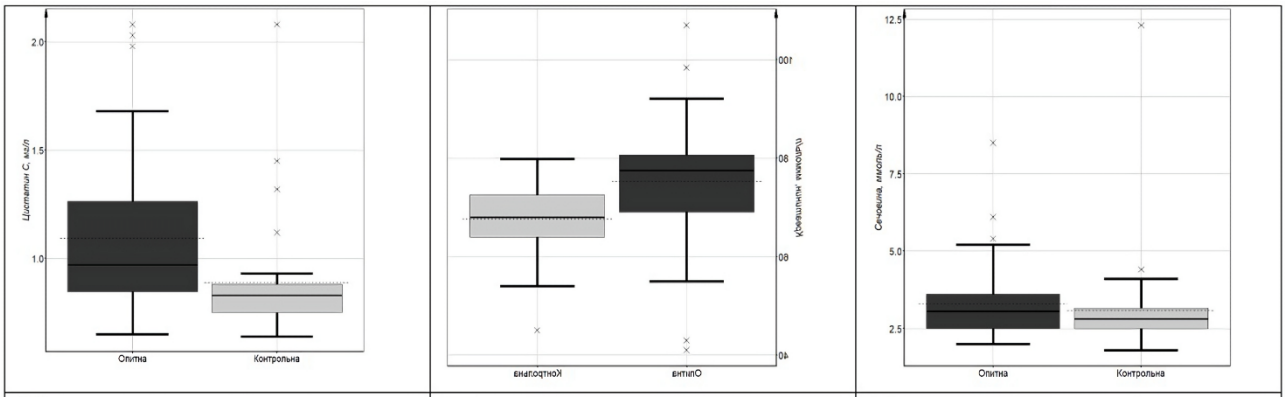
When we analyzed the obstetric history of 91 (100%) women, 36 (39.56%) had their first pregnancy; group I1 included 23 (25.27%) and 13 (14.29%) were I2. Of these, group IV1 included 13 first pregnancies (50%): eight pregnant women from group I1 and five from group I2 (practically healthy). Thus, of the known PE risk factors, the first pregnancy was the major factor in five (19.23%) of the 26 (100%) pregnant women in group IV1. When adjusting for PE with the first pregnancy, the odds ratio in the study was 1.83 (95% CI 0.73 to 4.59), sensitivity 76.36%, specificity 36.11%, and accuracy 60.44%. The most important effect on the development of PE in first-pregnant women from group I1 was noted when combined with chronic kidney disease (in six of eight first-pregnant women). In the analysis of the distribution of risk factors for pe in primiparous women, statistical significance was observed in association with chronic kidney disease-odds ratio (OR)=0.3 (95% CI 0.11 to 0.83) p=0.033. Risk factors such as age 35 years or older (HR=0.32 (95% CI 0.12 to 0.91), obesity (HR=0.65 [95% CI 0.2 to 2.04]), multiple pregnancies (HR=1.54 (95% CI 0.09 to 25.48), in vitro fertilization (HR=0.36 [95% CI 0.04 to 3.4]) and antiphospholipid syndrome (HR = 1.54 [95% CI 0.09 to 25.48]) were statistically insignificant (p>0.05). Thus, the most important influence on the development of PE in primiparous women belongs to a history of chronic kidney disease.

Adjusted obstetric factors that led to PE can be allocated in the direction of decreasing importance, as follows:

1. During previous pregnancy PE 6 (95% CI 0.88 to 40.87).
2. Multiple pregnancies VS 2.56 (95% CI 0.15 to 42.53).
3. First pregnancy 1.83 (95% CI 0.73 to 4.59).
4. ECO VSH 1.72 (95% CI 0.27 TO 10.96).
5. Maternal PE 1.57 (95% CI 0.35 to 7.08).
6. Interval ≥10 years between pregnancies WS 0.77 (95% DI 0.14-4.20).

Among extragenital diseases, the greatest influence on the development of PE was noted when combined with APS (HR 2.56 [95% CI 0.15 to 42.53]), whereas a history of kidney disease (HR 1 [95% CI 0.34 to 2.94]) and chronic hypertension (HR 0.18 [95% CI 0.02 to 2.08]) [34] were reported as low in our study.

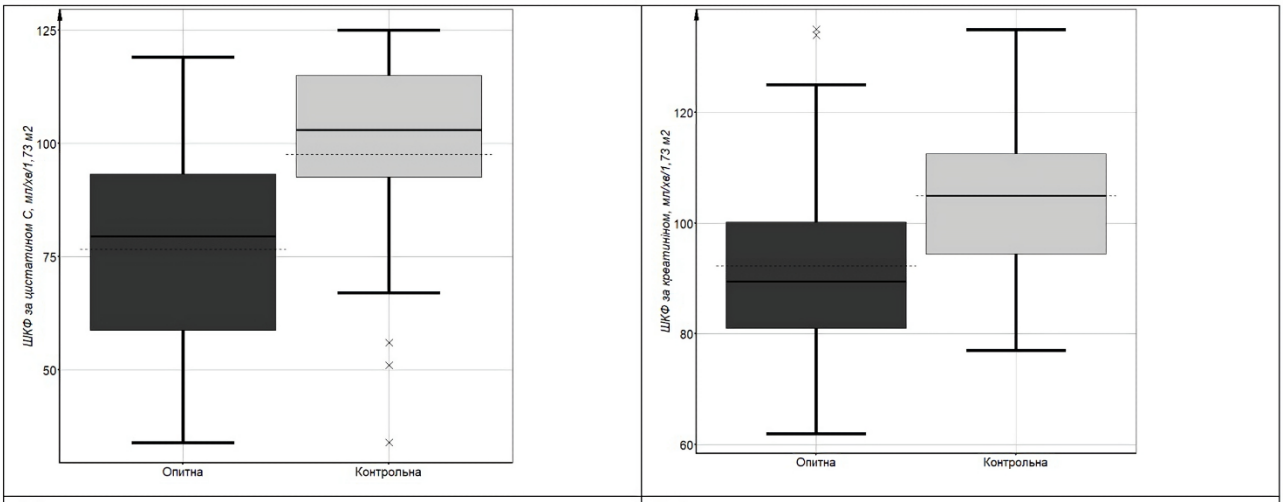
Thus, in our prospective study, the most important risk factor was PE in a previous pregnancy. Multiple pregnancy and antiphospholipid syndrome ranked second. However, when factors are combined, especially with chronic kidney disease and/or maternal characteristics, the risk of PE increases. In the



(a)	(b)	(c)
p*=0.003 dKoena=0.65 (95% CI: 0.55-0.75)	p*=0.001 dKoena=0.73 (95% CI: 0.62-0.83)	p=0.448 dKoena=0.16 (95% CI: 0.07-0.26)

Distribution of (a) cystatin C, (b) creatinine, and (c) urea values between survey (group I1) and control (group I2) groups; p*<0.05; immunoturbidimetric method, & n=91(47+44)

Figure 1. Comparison of cystatin C, creatinine, & urea levels among surveyed pregnant women between survey & control groups (Source: Authors' own elaboration)



(a)	(b)
p*<0.001 dKoena=0.96 (95% CI: 0.85-1.07)	p*<0.001 dKoena=0.84 (95% CI: 0.73-0.94)

Distribution of glomerular filtration rate values (a) by cystatin C and (b) by creatinine and between the experimental (I1 group) and control (I2 group) groups; p*<0.05; Immunoturbidimetric method; & n=91(47+44)

Figure 2. Comparison of glomerular filtration rate levels for cystatin C & creatinine among the surveyed pregnant women between the survey & control groups (Source: Authors' own elaboration)

analysis of maternal factors for development of PE, sensitivity is 37.50%, the specificity 85.71%, and the accuracy 56.04%.

Placental Characteristics and Their Influence on the Development of PE

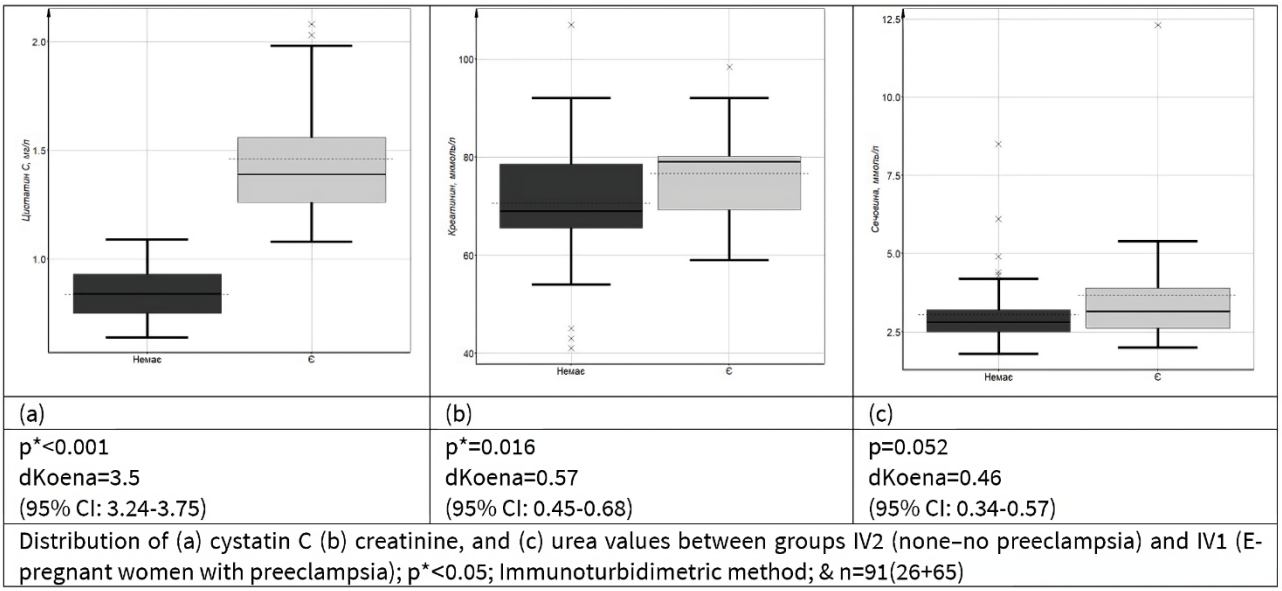
According to the results of our study, 47 (51.65%) pregnant women had the placenta located on the anterior uterine wall (II1) and 44 (48.35%) respectively on the posterior uterine wall (II2). Of these, the group IV1 (26 (28.57%) included 19 (20.88%) with the anterior location of the placenta and 7 (7.69%) with the posterior location. In calculating 100% equivalence: 73.07% for anterior placental location and 26.93% according to posterior placental location. .08%, accuracy 61.54% (p=0.019) Thus, we found that when the placenta is located along the anterior wall of the uterus, the risk of PE increases 3.59 times.

Cystatin C in the Preclinical Diagnosis of PE

Renal function markers (cystatin C, creatinine, and urea) were studied overnight at 18-36 weeks of gestation in pregnant women without clinical manifestations of PE. The mean serum cystatin C values in group I1 were 1.1±0.05 (95% CI: 1.01 to 1.19) and were significantly higher than those in I2 at 0.89±0.05 (95% CI: 0.79 to 0.98), (dCohene=0.65 [95% CI: 0.55 to 0.75], p=0.003) (**Figure 1**). This proves that the levels of cystatin C values were significantly and significantly elevated in the group of pregnant women at risk of PE compared with the control group. When calculating GFR by cystatin C, the mean levels in group I1 were 76.66±2.97 (95% CI: 70.84 to 82.48), indicating impaired renal filtration system, and in I2, 97.57±3.58 (95% CI: 90.56 to 104.59),

Table 2. Renal biomarker levels as a function of allocation to groups in PE screening (immunoturbidimetric method, n=91)

	Creatinine (µmol/l)	GFR by creatinine	Urea (mmol/l)	Cystatin Smg/L	GFR by cystatin C
I_1 (main)	75.24±1.59	92.34±2.17	3.31±0.16	1.10±0.05	76.66±2.97
I_2 (control)	67.56±1.34	104.97±2.21	3.08±0.29	0.89±0.05	97.57±3.58
II_1 (anterior location of placenta)	73.82±1.60	95.04±2.25	3.00±0.10	1.08±0.05	79.53±3.72
II_2 (posterior location of placenta)	70.64±1.70	99.50±2.56	3.46±0.28	0.95±0.05	90.23±3.20
IV_1 (got PE)	76.68±1.81	90.23±2.83	3.67±0.39	1.46±0.06	52.46±2.08
IV_2 (not got PE)	70.52±1.42	99.98±2.01	3.04±0.13	0.84±0.01	97.60±1.64
Σ	72.28±1.17	97.20±1.70	3.22±0.15	1.01±0.04	84.70±2.52
P	0.016	0.121	0.000	<0.001	0.001



(a)	(b)	(c)
p*<0.001 dKoena=3.5 (95% CI: 3.24-3.75)	p*=0.016 dKoena=0.57 (95% CI: 0.45-0.68)	p=0.052 dKoena=0.46 (95% CI: 0.34-0.57)

Distribution of (a) cystatin C (b) creatinine, and (c) urea values between groups IV2 (none–no preeclampsia) and IV1 (E-pregnant women with preeclampsia); p*<0.05; Immunoturbidimetric method; & n=91(26+65)

Figure 3. Comparison of cystatin C, creatinine, & urea levels among pregnant women examined between groups with & without PE (Source: Authors' own elaboration)

no renal function impairment. Statistical significance was Cohen's d=0.96 (95% CI: 0.85-1.07), p<0.001 (**Figure 2**).

Thus, it can be assumed that the risk of renal damage in pregnant women with a history of a poorer outcome is significantly higher than in healthy women and is highly likely to lead to the development of PE.

When comparing cystatin C and FFR values between groups II1 and II2, an increase in cystatin C over 1.0 mg/L was observed in group II1 (1.08±0.05), whereas in II2 the values did not exceed the normal reference values (0.95±0.05), which was also marked on the values of FFR-in group II1 the filtration capacity of the kidneys was reduced (79.53±3.72), and in group II2 the kidney function was not impaired (90.23±3.2) (**Table 2**).

Cystatin C levels were statistically significantly (p=0.001) different between groups IV1 and IV2. Thus, in group IV1 the value was 1.46±0.06 (95% CI: 1.35-1.57), i.e., at the preclinical stage of PE they exceeded the reference norm of 1.0 mg/l; in group IV2 the values were within the norm and were 0.84±0.01 (95% CI: 0.81-0.86) (**Figure 3**).

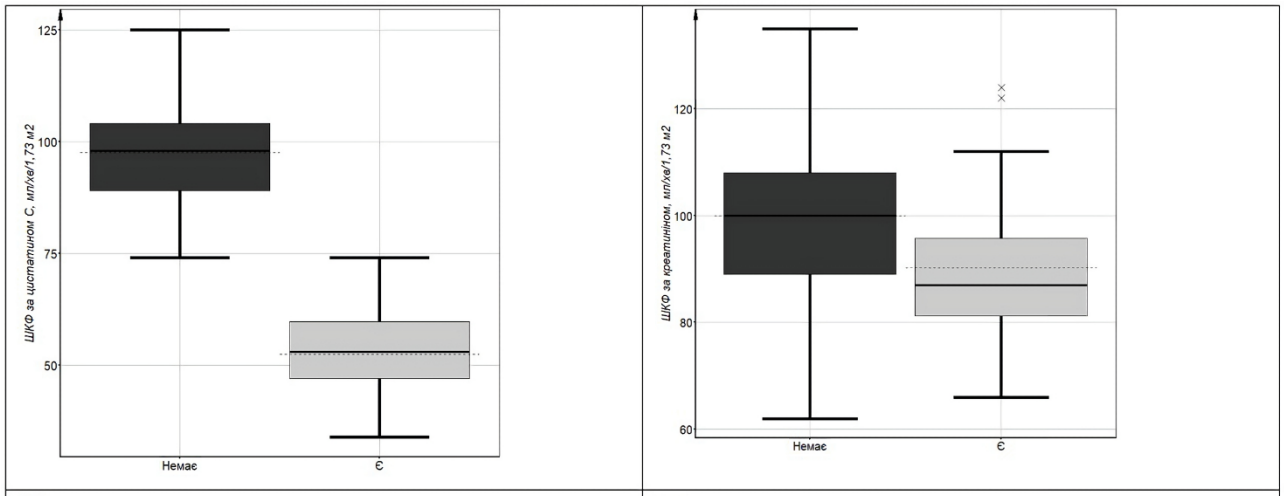
When calculating FFR by cystatin C, significant impairment of renal filtration system was noted in group IV1 -52.46±2.08 (95% CI: 48.39-56.54), while in group IV2 the value was within the norm -97.6±1.64 (95% CI: 94.38-100.82) (**Figure 4**).

Mean serum creatinine levels in the total group were 72.28±1.17 (95% CI: 69.99 to 74.57) with a glomerular filtration rate (GFR) of 92.34±2.17 of which pregnant women further developed pe, creatinine levels were 76.68±1.81 from a creatinine GFR of 90.23±2.83 and were within reference norm for healthy pregnant women. Serum urea levels in all study groups were within the reference norm for healthy pregnant women (**Table 2**).

Group III included 27 pregnant women. Of these, only one pregnant woman with a cystatin C1.0 level (1.09 mg/L) did not develop pe, because of the indication for an early operative delivery at 35 weeks of gestation (feto-fetal syndrome diagnosed). In the subgroup of pregnant women with cystatin C levels greater than 1.0 mg/L (27 women), pe developed in 26 women, or 96.29% in the percentage equivalent. There was a correlation in the rate of clinical symptomatology of PE in subgroup III1, namely, pregnant women with cystatin C levels of >1.85 mg/L developed clinical symptoms rapidly over one-two weeks, whereas those with cystatin C levels ≥1.08 mg/L developed clinical symptoms over five-seven weeks. When analyzing the ratio of cystatin C levels greater than 1.0 mg/L to the development of PE, a sensitivity of 98.46%, specificity of 100%, and accuracy of 98.9% were noted, p <0.001.

The odds ratio of the risk of cystatin C elevation adjusted with PE factors in the downward direction:

1. PE in a previous pregnancy-six (95% CI 0.88 to 40.87), p=0.146;
2. Anterior location of the placenta -3.92 (95% CI 1.45 to 10.57), p=0.011*,
3. Antiphospholipid syndrome -2.42 (95% CI 0.15 to 40.22), p=1;
4. First pregnancy, 2.06 (95% CI 0.82 to 5.13), p=0.186;
5. In vitro fertilization, 1.63 (95% CI 0.26 to 10.33), p=0.987;



(a)	(b)
p*<0.001 dKoena=3.6 (95% CI: 3.33-3.86)	p*=0.009 dKoena=0.62 (95% CI: 0.5-0.74)

Distribution of glomerular filtration rate values (a) for cystatin C and (b) for creatinine between groups IV2 (none–no preeclampsia) and IV1 (E-pregnant women with preeclampsia); p*<0.05; Immunoturbidimetric method; & n=91(26+65)

Figure 4. Comparison of glomerular filtration rate levels for cystatin C & creatinine among pregnant women examined between groups with and without PE (Source: Authors' own elaboration)

6. Obesity (BMI >30 kg/m^2), 1.54 (95% CI 0.5 to 4.78), p=0.65;
7. Maternal PE, 1.48 (95% CI 0.33 to 6.66), p=0.918;
8. A history of renal disease, 1.07 (95% CI 0.37 to 3.14), p=1;
9. Age 35 years or older, 1 (95% CI 0.37 to 2.67), p=1;
10. Pregnancy interval >10 years, 0.77 (95% CI 0.14 to 4.2), p=1;
11. Chronic hypertension, 0.19 (95% CI 0.02 to 2.2), p=0.412,
12. Multiple pregnancy -Inf (95% CII NaN-Inf), p=0.156.

According to the results of our study, the anterior location of the placenta statistically significantly increases by 3.92 times the risk of AKI during pregnancy, which may lead to the development of PE. Among the other maternal factors studied, the highest risk was noted in pregnant women with a history of PE in a previous delivery–the risk increased six-fold, but statistical significance in the isolated factor was not noted.

DISCUSSION

Numerous scientific studies have concluded that older age (35 years) and an increase in BMI before pregnancy (25 kg/m^2) are considered moderate risk factors for PE [25-31]. A high rate of PE is associated with the study selection of pregnant women with maternal risk factors according to FIGO recommendations [5]. Studies demonstrated an age dependence of PE development, with the authors suggesting in their conclusions that the highest risk is in women under the age of 20 and after 30 years [25].

Statins play an essential role in the human body, including during pregnancy. Statins as well as fatty acid sequestrants are effectively used to lower high-density lipoprotein cholesterol levels. The prescription of fibrates and nicotinic acid helps to reduce triglyceride levels and increase the above-mentioned lipoproteins. When using statins, the level of lipoproteins is reduced by more than 55%, triglycerides–by 7-30%. In addition, there is an increase in the concentration of lipoproteins–by 5-15% [32].

Being overweight and obesity before pregnancy are associated with an increased risk of PE [32]. Our findings are consistent with [33], which noted that tall women have the lowest rate of PE. Determination of the location of the placenta by ultrasound examination is one of the most accessible and noninvasive routine methods in obstetric practice. It is possible that the influence on the development of incomplete trophoblastic invasion, which leads to the release of markers such as fms-like tyrosine kinase type 1 (sFlt-1), vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) and contributes to endothelial dysfunction. in various organs [40, 41], there is an anatomic feature of unequal distribution of arterial inflow to the front and back uterine walls [23]. Our data confirm that at the preclinical stage of renal failure development, cystatin C is a reliable and early marker of endotheliosis and has high diagnostic significance in screening pe among such biomarkers as serum creatinine and urea [42].

Regarding the duration of pe, our data support other findings that the main pathological processes occur before delivery, but the risk of renal damage persists after delivery [41]. According to other data, the risk of PE persists during pregnancy if diabetic patients take vitamin C and aspirin [40]. Placental placement (lateral or central) does not affect the incidence of hypertension in patients [39], which is also confirmed by our data. On the other hand, the lateral location of the placenta indicates an increased likelihood of developing pe [38], which is also reflected in our results. Our results coincide with those of other authors who have found that the use of mid-trimester ultrasound screening techniques can predict the risk of pe [37]. Some authors link placental laterality and the high risk of hypertension in pregnant women [35, 36], which also coincides with our findings. The development of

eclampsia can also be associated with adolescence, and age over 35 years - with hypertension [28]. Thus, our work clearly shows the risk factors and presents a screening model for PE.

Future studies should investigate the influence of these factors in more detail, e.g., by considering the older maternal age (40 years and over). Similar studies of mothers with pathologies such as alcoholism and drug addiction are of some interest [43].

CONCLUSIONS

According to the results of our study, there is a close correlation of screening criteria for pe. We propose a three-component screening model for pe in the first, second, and third trimesters of pregnancy.

The first step is the collection of maternal anamnestic factors and the formation of risk groups for pe according to internationally accepted factors, which is done in the first trimester of pregnancy.

The second stage–during ultrasound screening in the second trimester of gestation, we suggest that pregnant women with anterior placenta be assigned to the risk group for the development of pe.

At the third stage, we recommend that pregnant women classified at the first and second stages to the pe risk group determine the serum cystatin C, a biomarker of AKI. A limitation of this study is the small sample size, so similar research on a larger sample is needed. In addition, the age of expectant mothers can also affect the results of the study, so this factor can also be a limitation of the study.

Author contributions: All authors have sufficiently contributed to the study and agreed with the results and conclusions.

Funding: No funding source is reported for this study.

Ethical statement: Authors stated that the study was approved at a meeting of the Ethical Committee of the Odessa Medical Institute (Minutes of Meeting No. 12-1).

Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

REFERENCES

1. Bibbins-Domingo K. Screening for preeclampsia US preventive services task force recommendation statement. JAMA. 2017;317(16):1661-7. https://doi.org/10.1001/jama.2017.3439 PMid:28444286
2. NICE. Hypertension in pregnancy: Diagnosis and management. National Institute for Health and Care Excellence; 2019. Available at: www.nice.org.uk/guidance/ng133 (Accessed: 21 September 2020).
3. American Diabetes Association. Management of diabetes in pregnancy: Standards of medical care in diabetes-2019. Care. 2019;42(Suppl1):165-72. https://doi.org/10.2337/dc19-S014 PMid:30559240
4. Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension. 2018;72:24-43. https://doi.org/10.1161/HYPERTENSIONAHA.117.10803 PMid:29899139
5. Poon LC, Shennan A, Hyett JA, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol. 2019;145(1):1-33. https://doi.org/10.1002/ijgo.12802 PMid:31111484 PMCid:PMC6944283
6. Poon LC, Rolnik DL, Tan MY, et al. ASPRE trial: Incidence of preterm preeclampsia in patients fulfilling ACOG and NICE criteria according to risk by FMF algorithm. Ultrasound Obstet Gynecol. 2018;51:738-42. https://doi.org/10.1002/uog.19019 PMid:29380918
7. American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 222 summary: Gestational hypertension and preeclampsia. Obstet Gynecol. 2020;135(6):237-60. https://doi.org/10.1097/AOG.0000000000003891 PMid:32443079
8. Giles LA. Implementing screening guidelines for preeclampsia prevention in a birth center: A quality improvement project. J Perinat Neonatal Nurs. 2020;34(4):324-9. https://doi.org/10.1097/JPN.0000000000000489 PMid:32804877
9. Guy GP, Leslie K, Diaz-Gomez D, et al. Implementation of routine first trimester combined screening for pre-eclampsia: A clinical effectiveness study. BJOG. 2021;128(2):149-56. https://doi.org/10.1111/1471-0528.16361 PMid:32613730
10. FIGO. International Federation of Gynecology and Obstetrics; 2022. Available at: https://www.figo.org/figo-releases-newguidelines-combat-pre-eclampsia (Accessed: 12 September 2022).
11. Shlipak MG, Tummalapalli SL, Boulware LE, et al. The case for early identi fi cation and intervention of chronic kidney disease: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2021;99:34-47. https://doi.org/10.1016/j.kint.2020.10.012 PMid:33127436
12. Bellos I, Fitrou G, Daskalakis G, Papantoniou N, Pergialotis V. Serum cystatin-C as a predictive factor of preeclampsia: a meta-analysis of 27 observational studies. Pregnancy Hypertens. 2019;16:97-104. https://doi.org/10.1016/j.preghy.2019.03.006 PMid:31056166
13. Szczepanski J, Griffin A, Novotny S, Wallace K. Acute kidney injury in pregnancies complicated with pre-eclampsia or HELLP syndrome. Front Med. 2022;7:22. https://doi.org/10.3389/fmed.2020.00022 PMid:32118007 PMCid:PMC7020199
14. Vijayalakshmi P, Usha SMR. Assessment of serum cystatin C and creatinine in monitoring pre-eclampsia. JCDR. 2019;13(6):12-5. https://doi.org/10.7860/JCDR/2019/41385.12923
15. Digambarrao DJ, Pramod WI, Varsha BH. Cystatin C in preeclampsia: A case control study Int J Curr Res. 2015;7(7):18226-30.
16. Kreepala C, Srila-on A, Kitporntheranunt M, Anakkamatee W, Lawtongkum P, Wattanavaekin P. The association between GFR evaluated by serum cystatin C and proteinuria during pregnancy. Kidney Int Rep. 2019;4:854-63. https://doi.org/10.1016/j.ekir.2019.04.004 PMid:31194092 PMCid:PMC6551540
17. Ebert N, Shlipak MG. Cystatin C is ready for clinical use. Curr Opin Nephrol Hypertens. 2020;29:591-8. https://doi.org/10.1097/MNH.0000000000000638 PMid:32868529

18. Popkov VA, Andrianova NV, Manskikh VN, et al. Pregnancy protects the kidney from acute ischemic injury. Sci Rep. 2018;8:14534. https://doi.org/10.1038/s41598-018-32801-8 PMid:30266919 PMCid:PMC6162317
19. Conti-Ramsden FI, Nathan HL, De greeff A, et al. Pregnancy-related acute kidney injury in preeclampsia. Hypertension. 2019;74(5):1144-51. https://doi.org/10.1161/HYPERTENSIONAHA.119.13089 PMid:31564161 PMCid:PMC6791560
20. Park S, Lee SM, Park JS, et al. Midterm eGFR and adverse pregnancy outcomes: The clinical significance of gestational hyperfiltration. Clin J Am Soc Nephrol. 2017;12:1048-56. https://doi.org/10.2215/CJN.12101116 PMid:28611078 PMCid:PMC5498359
21. KDIGO. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. KI. 2021;100:1-276.
22. Wattanavaekin K, Kitporntheranunt M, Kreepala C. Cystatin C as a novel predictor of preterm labor in severe preeclampsia. Kidney Res Clin Pract. 2018;37(4):338-46. https://doi.org/10.23876/j.krcp.18.0080 PMid:30619689 PMCid:PMC6312773
23. Kozlov SV, Dvoretskyi DD, Alekseenko LA, Omelchenko A, Kartamышeva VD. Variant anatomy of the uterine arteries. UWMBS. 2018;3-4(13):32-7. https://doi.org/10.26693/jmbs03.04.032
24. Priyadarshini A, Upreti P, Nautiyal R, Goyal M. Placental location and development of preeclampsia: A longitudinal study. Int J Reprod Contracept Obstet Gynecol. 2019;8(4):1283-7. https://doi.org/10.18203/2320-1770.ijrcog20191005
25. Kumari N, Dash K, Singh R. Relationship between maternal age and preeclampsia. IOSR-JDMS. 2016;15(12):55-7.
26. Quan LM, Xu QL, Zhang GQ, Wu LL, Xu H. An analysis of the risk factors of preeclampsia and prediction based on combined biochemical indexes. Kaohsiung J Med Sci. 2018;34:109-12. https://doi.org/10.1016/j.kjms.2017.10.001 PMid:29413226
27. Walker KF, Thornton JG. Advanced maternal age. Obstet Gynaecol Reprod Med. 2016;26:354-7. https://doi.org/10.1016/j.ogrm.2016.09.005
28. Ndiaye MD, Guèye M, Diallo M, et al. The impact of extreme maternal ages on hypertensive disorders of pregnancy: A retrospective cohort study in Dakar, Senegal. OJOG. 2020;10:213-20.https://doi.org/10.4236/ojog.2020.1020018
29. Habek C, Bobik MV, Habek D, Gulin D, Gulin S. Pregestational obesity–risk factor for preeclampsia. Med Jad. 2019;49(1):45-9.
30. Poorolajal J, Jenabi E. The association between body mass index and preeclampsia: A meta-analysis. J Matern Fetal Neonatal Med. 2016;29(22):3670-6. https://doi.org/10.3109/14767058.2016.1140738 PMid:26762770
31. Hussain W, Khan HA, Imran M. Obesity: A risk factor of preeclampsia. Int J Front Sci. 2019;3(2):104-7. https://doi.org/10.37978/tijfs.v3i2.55
32. Chen C-N, Chen HS, Hsu HC. Maternal prepregnancy body mass index, gestational weight gain, and risk of adverse perinatal outcomes in Taiwan: A population-based birth cohort study. Int J Environ Res Public Health. 2020;17(4):1221. https://doi.org/10.3390/ijerph17041221 PMid:32074959 PMCid:PMC7068269
33. Lee Y, Magnus P. Maternal and paternal height and the risk of preeclampsia. Hypertension. 2018;71:666-70. https://doi.org/10.1161/HYPERTENSIONAHA.117.10477 PMid:29463626
34. Berlinska LI, Marichereda VG, Holubenko MY, Pavlovska OM. Maternal factors of pre-eclampsia development. RE. 2021;2(59):102-6. https://doi.org/10.18370/2309-4117.2021.58.102-106
35. Nair VV, Nair SS, Radhamany K. Study of placental location and pregnancy outcome. Int J Reprod Contracept Obstet Gynecol. 2019;8(4):1393-7. https://doi.org/10.18203/2320-1770.ijrcog20191187
36. Prathima A, Reddi Rani P. Association of placental position with the development of hypertension in pregnancy. Int J Reprod Contracept Obstet Gynecol. 2018;8(1):238-42. https://doi.org/10.18203/2320-1770.ijrcog20185431
37. Keshavarz E, Sadeghian A, Hakemi AG, Khtibi FT. Prediction of pre-eclampsia development by placenta location: A simple predictor. J ObstetGynecol Cancer Res. 2017;2(4):e11945. https://doi.org/10.5812/jogcr.11945
38. Rai A, Thatal A, Sharma BK, Narwat Y. Lateral placenta as a predictor for the development of preeclampsia. IJOGR. 2020;7(2):216-21. https://doi.org/10.18231/j.ijogr.2020.045
39. Salama-Bello R, Duncan JR, Howard SL, Song J, Schenone MH. Placental location and the development of hypertensive disorders of pregnancy. J Ultrasound Med. 2019;38:173-7. https://doi.org/10.1002/jum.14681 PMid:29732593
40. Navolotskaya VK, Lyashko ES, Shifman EM, et al. Possibilities for prediction of preeclampsia complications. Russ J Hum Reprod. 2019;25(1):20-9. https://doi.org/10.17116/repro20192501187
41. Sani HM, Vahed SZ, Ardalan M. Preeclampsia: A close look at renal dysfunction. Biomed Pharmacother. 2019;109:408-16. https://doi.org/10.1016/j.biopha.2018.10.082 PMid:30399576
42. Marichereda VH, Holubenko MIu, Berlinska LI. Priority of cystatin C among renal biomarkers in the diagnosis of preeclampsia. Kidneys. 2020;9(2):87-91. https://doi.org/10.22141/2307-1257.9.2.2020.203407
43. Napryeyenko O, Napryeyenko N, Marazziti D, et al. Depressive syndromes associated with alcohol dependence. Clin Neuropsychiatry. 2019;16(5-6):206-12.