INTRODUCTION
Preeclampsia (PE) is one of the main causes of complications during pregnancy, leading to maternal and perinatal morbidity and mortality, especially at early stages. The prevalence of PE varies from 2% to 5% among pregnant women and depends on the level of development in various countries worldwide [1]. There is evidence that women who had PE at older have an increased risk of death associated with cardiovascular disease, hypertension, stroke, renal failure, metabolic syndrome, and diabetes [2, 3]. Female’s life expectancy is reduced by 10 years in average. Despite the number of potential factors studies, the etiology of PE is not reduced to a single mechanism that leads to a cascade of successive events resulting in multiple organ failure. The priority of the international professional community is to improve the identification of women at high risk for PE in order to initiate the necessary preventive measures targeting reduction of morbidity and improvement of placentation. It is recommended to conduct a universal comprehensive screening at early gestation period by the end of the first trimester for all pregnant women, which includes the identification of risk factors and biomarkers. According to the recommendations of the Federation International of Gynecologists and Obstetricians (FIGO), high PE in previous births, chronic hypertension, type 1 or 2 diabetes, kidney disease, autoimmune diseases, multiple pregnancies) and moderate (no birth history, obesity, family history of PE, family history of PE, age over 35 years, interval between pregnancies over 10 years and more, in vitro fertilization (IVF)) risk factors for PE [1]. At present, in order to improve the prediction of PE at the initial stage of treatment, the urgent problem is to determine the most important maternal factors. This can help reduce the development and reduce the incidence of PE complications through timely prevention and treatment.

Study objective: to determine the most important maternal factors for PE predicting, which are used in screening of women when registered for pregnancy.

MATERIALS AND METHODS
In 2018–2020 a prospective cohort study of 91 pregnant women in the first trimester of gestation was conducted on the basis of the Women’s Clinic and Obstetric Hospital of KU Maternity Hospital №2 (Odesa), as well as at the medical commercial laboratory. Study group included 56 (61.54%) women in the main group who according to the FIGO recommendations (2019) had a number of maternal factors associated with PE development, and 35 (38.46%) women in control group were healthy. Study group included pregnant women with the following factors: history of kidney disease – 21 patients (23.08%), PE during previous pregnancies – 5 patients (9.09%), multiple pregnancies – 2 patients (2.2%), chronic hypertension – 3 patients (33%); antiphospholipid syndrome (APS) – 2 patients (2.2%); IVF – 5 patients (5.49%); first pregnancy 23 (25.27%), body mass index (BMI) > 30 kg/m² before pregnancy 15 (16.48%), >35 years aged women – 22 patients (24.18%), PE in mother – 8 patients (8.79%), the interval of previous pregnancy > 10 years – 9 patients (8.19%) (Table).

The general exclusion criteria were cancer, tuberculosis, severe somatic pathology at the stage of decompensation, mental disease, chronic alcoholism, drug addiction and trauma during pregnancy, which led to obstetric complications.

Further division into subgroups was based on the International Society for the Study of Hypertension in Pregnancy recommendations (ISSHP) and approved by the FIGO for PE detection [1, 4]. PE was determined by systolic blood pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg when measured at least 2 times every 4 hours in women who had normal blood pressure prior to pregnancy, or with the following conditions detected at 20th gestation week or later: proteinuria (≥30 mg/mol) or other pathological conditions, including acute renal failure (creatinine level ≥90 µmol/l), liver disease with or without pain in the right upper quadrant of the abdomen or epigastic pain, neurological or hematological complications, utero-placental dysfunction. Thus 28.57% of pregnant women were included into PE subgroup, and 71.43% were women who had no PE.

Statistical analysis
The data obtained in the study were entered into the MS-Excel database and analyzed using the statistical program MedCalc for PC, version 12.7.0 (MedCalc Software, Belgium). Descriptive analysis was used for intergroup comparison to determine the most important factors in the development of PE. Receiver operating characteristic (ROC) with area under the curve (AUC) were used. Group comparisons were performed using one of the ANOVA methods. A value of p <0.05 was considered statistically significant.

RESULTS AND DISCUSSION
As for the 100% of study group, PE has been found in 26 (28.57%) of pregnant women: 21 (23.08%) in the main group and 5 (5.49%) in the control group. The average age of pregnant wom-
en of 30 years is steadily increasing. Women over the age of 35 had an increased risk of maternal and perinatal complications; the most dangerous was PE [5]. The age distribution of women in the study group was 15–42 years, the average age was 30.53 ± 0.62 (95% confidence interval (CI): 29.3–31.75, p = 0.006); the age distribution in the main group was 31.88 ± 0.86 (95% CI: 30.19–33.56) and was higher compared to control group 28.37 ± 0.74 (95% CI: 26.92–29.82). The following statistical difference was found between subgroups of women who developed PE (30.65 ± 1.25, 95% CI: 29.63–31.64) and without PE (31.83 ± 1.12, 95% CI: 30.65–33.04) and in the control group (28.9 ± 0.78, 95% CI: 27.36–30.44), F =2,009, η² = 0.044, p =0.14. The average age of women in the subgroups did not differ (p >0.05) (Fig. 1).

ROC did not show a significant difference in AUC when analyzing the age of pregnant women in relation to PE: in women with PE AUC was 0.54, in women without PE it was 0.46; therefore the quality of model is not satisfactory. Thus, the direct association between PE and age increase in our study has not been confirmed.

Number of women over 35 years in the main group was 27 (29.67%), with 8 (8.79%) developing PE (Fig. 2). There is no statistical significance between women older than 35 years and older women in the PE risk (p >0.05). Thus, the analysis of study data did not confirm an association of age 35–42 years with PE development. Our results are consistent with studies by M. Ndiaye et al.: they reported that the age >35 is associated with 1.6 fold increase of high blood pressure compared with women from 19–34 years aged group before and after adjustment for parity, multiple pregnancy and diabetes. However, the eclampsia risk is 4 times higher in women under 35, especially in adolescents who do not have additional risks of high blood pressure [6].

The growing trend for obesity worldwide in terms of prevalence among pregnant women is 15–38%. The exact mechanisms of obesity and PE association are not clear yet. Hyperinsulinemia plays an important role in the pathogenesis of PE in overweight patients. The central nervous system and kidneys remain sensitive to insulin, while hyperinsulinemia is a factor that activates the sympathetic division of the autonomic nervous system and increased vascular tones. Under conditions of sympahticotonia, the filtration of glucose by glomeruli increases, which leads to increased reabsorption of sodium in the proximal tubules of the nephron. It results in fluid and electrolytes retention. The direct action of insulin under the conditions of hyperinsulinemia also helps to reduce the level of intracellular potassium and to increase the level of calcium and sodium. The
effect of catecholamines is significantly increased. It is believed that endothelial dysfunction, microthrombosis and hyper-insulinemia in obese women lead to impaired implantation, trophoblast invasion and placentation, which can further lead to the development and severe course of PE. J. Čerkez Habek et al. demonstrated statistically significant differences in BMI between groups of females with PE and control groups at the middle gestation age, as well as in the average pre-gestation values of BMI. The authors suggest that increased pre-gestation BMI is a risk of PE during pregnancy [7]. In order to assess the association between overweight or obesity and PE, J. Poorolajal and E. Jenabi conducted a meta-analysis that included 23 studies with 1,387,599 participants. PE was associated with overweight (OR (odds ratio) = 1.73; 95% CI: 1.59–1.87; 21 studies) and obesity (OR = 3.15; 95% CI: 2.96–3.35; 22 studies). The authors report that the index of excess body weight is significantly associated with an increased PE risk. Therefore, overweight and obesity can be considered as a PE predictor [8].

The average weight of women before pregnancy in the main group in our study was 73.69 ± 2.48 kg (95% CI: 68.83–78.54) with a BMI of 26.7 ± 0.86 (95% CI: 25–28.39), while in the control group body weight was 61.85 ± 1.48 kg (95% CI: 58.96–64.75) and BMI was 22.5 ± 0.59 (95% CI: 21.35–23.65); thus in women with PE risk there was a statistically significant increased weight and BMI compared to healthy pregnant women (p <0.001). Women who subsequently developed PE had body weight 71.8 ± 3.66 kg (95% CI: 64.63–78.98) with a BMI 26.83 ± 1.29 (95% CI: 24.31–29.36), the average weight of pregnant women without PE was 73 ± 3.08 kg (95% CI: 65.37–87.63) with a BMI 26.03 ± 1.05 (95% CI: 23.98–28); in the control group the respective values were 62.32 ± 1.67 kg (95% CI: 59.05–65.58) with a BMI 22.46 ± 0.67 (95% CI: 21.16–23.77) with a statistical significant difference of p-values for weight (p <0.05) and BMI (p <0.05, F = 5.028, \( \chi^2 = 0.0103 \)). The ROC analysis of AUC of BMI for PE in pregnant women showed an average quality (0.62) in women with PE, and there has been unsatisfactory in pregnant women without PE (0.57) and in the control group (0.32), which proves BMI association with the PE development.

The frequency of obesity among pregnant women was 16 (17.58%), PE has been developed in 6 (6.59%) women, of whom the first degree of obesity was reported in 3 females (3.3%), the second degree has been reported in 1 female (1.1%) and the third degree has been reported in 2 females (2.2%) (Fig. 2). There was no statistical significance for PE development associated with the obesity degree (Pearson's agreement criterion 1.37, p <0.05). Thus, in our study we found a direct proportional association between the PE development and an increased BMI before pregnancy, even in overweight; however, the association with the obesity degree has not been demonstrated. This is consistent with the conclusions of other authors [7–10].

Height comparison between women from the main group (166.05 ± 0.81 cm, 95% CI: 164.46–167.65) and the control group (166.23 ± 1.74 cm, 95% CI: 162.82–169.64) demonstrated no statistical difference (p >0.05). Statistically significant results were observed between women who developed PE (163.35 ± 1.26 cm, 95% CI: 160.87–165.82) compared to women who did not develop PE (167.23 ± 1.02 cm, 95% CI: 165.23–169.2), p <0.05, Cohen’s index 0.5 (95% CI: 0.38–0.62). ROC showed a significant difference in AUC in pregnant women with PE – 0.28 and without PE – 0.72. It can be assumed that women with lower height have an increased PE risk (Fig. 1). The association between maternal lower height and PE has also been confirmed in previous studies [11, 12].

The first pregnancy is one of the leading factors in the PE development, which accounts for 4.1%; it is believed that the influence of the new antigen is involved in the pathogenesis. Our study included 36 (39.56%) women with first pregnancy, 23 (25.27%) of which in the main group and 13 (14.29%) in the control group; PE has been developed in 13 (14.29%) pregnant women, but no statistical significance has been reported (p >0.05) (Fig. 2). Among the risk factors that led to PE, statistically significant results were observed when combining the first pregnancy with a history of kidney disease (p <0.05) and reached 13 (14.29%). Risk factors such as age >35 years were reported in 6 females (6.59%), obesity – in 5 females (5.49%), PE in the mother has been reported in 5 females (5.49%), multiple pregnancy – in 1 female (1.1%), IVF – in 1 female (1.1%) and antiphospholipid syndrome – in 1 female (1.1%) were statistically insignificant. Thus, the most significant influence on the development of PE in first time pregnant women is a history of chronic kidney disease.

PE prevalence of in subsequent pregnancies was also reported in 13 females (14.29%). Thus, PE is influenced not only by the new antigen, but also by other factors influencing the development of endoeliosis. The increased risk of PE recurrence in subsequent pregnancies is associated with diastolic blood pressure levels and early onset in the first pregnancy, namely the risk increases proportionally [13, 14]. In our study, recurrent PE was reported in 3 females (5.45%), statistically significant results were observed when combined with PE in mother, p = 0.011 (Fig. 2). PE risk is considered lower during the second pregnancy if the fetus is conceived with the same partner, but the chances of PE is increased along with the interval between labors. Women with intervals between pregnancies over 6 years have a higher risk of developing PE.
The analysis identified risk factors for PE development (risk decrease sequence):

1. PE during a previous pregnancy: OR = 6 (95% CI 0.88–40.87).
2. Multiple pregnancy: OR = 2.56 (95% CI 0.15–42.53) and APS: OR = 2.56 (95% CI 0.15–42.53).
3. The first pregnancy: OR = 1.83 (95% CI 0.73–4.59).
4. IVF: OR = 1.72 (95% CI 0.27–10.96).
5. Obesity (BMI >30 kg/m²): OR = 1.65 (95% CI 0.53–5.13).
6. PE in the mother: OR = 1.57 (95% CI 0.35–7.08).
7. Age ≥35 years: OR = 1.08 (95% CI 0.4–2.89).
8. History of renal disease: OR = 1 (95% CI 0.34–2.94).
9. Interval between pregnancies >10 years: OR = 0.77 (95% CI 0.14–4.2).
10. Chronic hypertension: OR = 0.18 (95% CI 0.02–2.08).

CONCLUSIONS

The most important risk factor in our prospective study is PE during previous pregnancy. The second position is occupied by multiple pregnancy and APS. These factors, according to the FIGO recommendations are classified as high risk factors. The first pregnancy, IVF, pre-gestation obesity, the age of pregnant woman >35 years (OR is less than 2 but more than 1) are classified as moderate factors and coincide with the factors proposed by the communities.

A history of renal disease and chronic hypertension, which is also a high risk factor, were not significant in our study with OR <1. However, when factors are combined, especially with chronic renal disease and/or elevated BMI, the PE risk is increases.

Thus, we have demonstrated that thorough monitoring of maternal risk factors helps to predict the PE development, but for more sensitive and specific detection it is necessary to use complex models based on biochemical and Doppler indicators.

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МАТЕРИНСЬКИ ЧИННИКИ В РОЗВИТКУ ПРЕЕКЛАМПСІЇ

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Матеріали та методи. У рамках дослідження визначено материнські фактори прогнозування прееклампсії (ПЕ), які використовуються в скрінінгу жінок при постановці на облік за вагітністю.

Використання єдиного артеріального гіпертензії на розвиток ПЕ відзначено при тривалості захворювання понад 5 років. Інтервал між вагітностями 10 та більше років у розвитку ПЕ відзначено з використання вагітних старше 35 років (p = 0.01). При екстракорпоральному заплідненні ПЕ відзначено з використанням малорічних жінок, які мають інтервал між першою вагітністю i вагітністю 35 років. Результати відшукано у жінок з вагітністю старше 35 років від попередньої вагітності.

Висновки. При рельєфному моніторингу материнських факторів ризику ПЕ в нашому дослідженні найважливішими чинниками є старість жінок під час попередньої вагітності та артеріальна гіпертензія. Особливість підходу при постановці на облік за вагітністю вимагає уваги.

Ключові слова: прееклампсія, ожиріння, зріст, перша вагітність, хронічні захворювання нирок.