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Early-Versus Late-Onset Preeclampsia: Differences in Risk Factors and Birth Outcomes

Introduction. Preeclampsia (PE) continues to be the leading cause of maternal and fetal morbidity and mortality worldwide with an incidence of 3.0–5.0 % [1, 6, 8, 10]. It is responsible for approximately 76,000 maternal deaths and 500,000 infant deaths per year worldwide [7, 4].

PE represents one of the most common causes of maternal mortality and severe maternal morbidity including eclampsia, placental abruption, pulmonary edema, and acute renal failure. Infants of mothers with preeclampsia are at approximately 2-fold higher risk of neonatal death and at increased risk of neonatal morbidity including low V. Apgar scores, seizures, neonatal encephalopathy, and neonatal intensive care admission [5, 7].

In the past 30 years, a large amount of research has been performed to investigate the pathogenesis and pathophysiology of preeclampsia. Despite that, understanding of these processes has increased strikingly, the ability to manage PE has not improved accordingly. Proof of this is the fact that the diagnostic criteria of PE are still based on unspecific clinical, ultrasound and laboratory findings, rather than on their pathogenic origin, and such diagnostic criteria have scarcely been modified over the past decades [4, 10].

As a paradigm, the current gold standard of PE diagnosis relies on the demonstration of new-onset of hypertension and proteinuria in the second half of pregnancy, whose presence does not always precede the onset of complications and has no predictive ability of PE-related adverse outcomes.

Recently evidence suggests that PE can be subdivided into early-onset PE (EOP), requiring delivery before 34 weeks gestation and late-onset PE (LOP), with delivery at or after 34 weeks, because the former is associated with a higher incidence of adverse outcome [2, 3, 5–7, 9]. They are associated with different maternal and fetal outcomes, biochemical markers, heritability, and clinical features. Although the diagnostic criteria are the same in each of these phenotypic variants of preeclampsia, they are characterized by different clinical features and are associated with different maternal and fetal outcomes [5–9].

Within the context of personalized medicine, future lines for investigations dealing with the prediction and prevention of PE should be based on the identification of the PE subtypes with regard to the maternal characteristics and clinical factors.

We carried out a case-control study to describe the gestational age specific incidence of preeclampsia onset among women with singleton pregnancies and to examine risk factors and birth outcomes associated with early-onset and late-onset disease. Therefore, our objective was to evaluate similarities and differences on clinical findings in patients with EOP and LOP.

The aim of this study was to study the incidence of early-onset and late-onset preeclampsia at a tertiary care center (at obstetrical department of L'viv Regional Clinical Hospital) and to find the difference in risk factors and birth outcomes associated with early-onset and late-onset preeclampsia.

Materials and methods. A case-control study was performed at obstetric department of L'viv Regional Clinical Hospital over a 3-year period (June 2015 - June 2017). Clinical and anamnestic data were analyzed for 300 pregnant women aged 16-43 years old with singleton pregnancies divided into 3 groups: group I consisted of 100 patients with EOP, group II – 100 patients with LOP; group III (control) consisted of 100 normotensive pregnant women who delivered consecutively after preeclamptic pregnant women.

PE was defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy [4]. EOP was defined as onset of disease from 20 weeks 0 days to 33 weeks 6 days, whereas LOP was regarded as PE after 34 weeks' gestation. Gestational age was determined by the last normal menstrual period, or ultrasound when performed at 11 weeks 0 days to 13 weeks 6 days weeks' gestation.

Hospitalization records with the diagnosis of PE were linked to birth records to obtain information about gestational age at delivery, maternal characteristics, clinical risk factors, and birth outcomes.

Maternal and clinical risk factors include maternal age, parity, previous PE, body mass index (BMI) more than 25kg/m^2, smoking during pregnancy, infertility treatment, congenital anomalies and pre-existing medical conditions such as chronic hypertension, diabetes mellitus.

Perinatal characteristics and birth outcomes including small-for-gestational-age (SGA) fetus, gestational age at delivery in weeks, preterm delivery, birthweight (g), Cesarean delivery, V. Apgar scores at 1 min <7, V. Apgar scores at 5 min <7, neonatal intensive care unit (NICU) admission, severe neonatal morbidity, fetal, neonatal, perinatal death. SGA infants were defined as those weighing less than the 10th percentile of the gestational age. Severe neonatal morbidity included any of the following: neonatal seizures, bronchopulmonary dysplasia, intraventricular hemorrhage grade III and IV, periventricular leukomalacia, retinopathy of prematurity, necrotizing enterocolitis, and neonatal sepsis. Fetal death was defined as in utero or intrapartum death of a fetus delivered at 22 weeks' gestation or later, neonatal death was defined as a death of an infant within 28 days after birth, and perinatal death included fetal and early neonatal death (death of an infant within 7 days after birth).

Statistical data were processed using Statistica 8.0 suite. Differences between the compared values were considered significant at $p < 0.05$.

This investigation conforms to the principles outlined in the Declaration of Helsinki.

Results of the investigation and their discussion. The study included 300 women who delivered a singleton live birth or stillbirth at obstetric department of L'viv Regional Clinical Hospital during the 3-year period (June 2014 - June 2017).

Comparison of maternal characteristics and clinical factors associated with EOP and LOP is shown in Table 1.

Table 1

Maternal characteristics and clinical factors in early-onset and late-onset preeclampsia and no preeclampsia groups

Maternal characteristics/clinical factors	I group (EOP) (n = 100)	II group (LOP) (n = 100)	III group (Control) (n = 100)
Age, year <20 20-34 ≥35	 6 74 20	 16 68 16	 6 90 4
Number of prior live births 0 ≥1	 48 52	 74 26	 40 60
Previous preeclamptic pregnancy	2	4	2
Smoking during pregnancy	10	10	2
Infertility treatment	4	6	2
Pre-pregnancy BMI greater than	24	12	4
Diabetes mellitus	2	12	2
Chronic hypertension	20	10	1
Congenital anomalies	4	0	0

Several risk factors were associated with PE, without the significant difference for early and late-onset disease. Maternal age more than 35 years (20.0 %, 16.0 %, and 4.0 % in the EOP, LOP and no preeclampsia groups, respectively, $p < 0.0001$), smoking during pregnancy (10.0 %, 10.0 %, and 2.0 %, $p < 0.02$), pregestational BMI greater than 25 kg/m^2 (24.0 %, 12.0 %, and 4.0 %, $p < 0.008$), chronic hypertension (20.0 %, 10.0 %, and 1.0 %, $p < 0.001$), were significantly associated with the increased risk of both early and late onset preeclampsia.

Several risk factors differed significantly in their association with EOP vs LOP. Women with diabetes mellitus (2.0 % vs 12.0 % in the EOP vs LOP groups, $p < 0.001$), nulliparity (48.0 % vs 74.0 %, $p < 0.001$), young women (younger than 20 years) (6.0 % vs 16.0 %, $p < 0.02$) were significantly associated with the increased risk of LOP. Chronic hypertension (20.0 % vs 10.0 % in the EOP vs LOP groups, respectively, $p < 0.01$), and congenital anomalies (4.0 % vs 0.0 %, $p < 0.04$), were more strongly associated with EOP. No statistically significant differences were seen on admission between the groups in the rate of the prior pregnancy with hypertension, and infertility treatment. Perinatal characteristics are shown in Table 2.

Table 2

Perinatal characteristics and birth outcomes in early-onset and late-onset preeclampsia and no preeclampsia groups

Perinatal characteristics and birth outcomes	I group (EOP) (n = 100)	II group (LOP) (n = 100)	III group (Control) (n = 100)
SGA (<10th percentile)	32	16	6
Gestational age at delivery (weeks)	30.5 ± 3.3	37.0 ± 2.2	37.6 ± 3.7
Preterm delivery	100	22	8
Birthweight (g)	1569.6 ± 537.2	2689.8 ± 597.3	2981.2 ± 742.1
Cesarean delivery	90	48	8
V. Apgar scores at 1 min <7	36	6	4
V. Apgar scores at 5 min <7	10	2	0
NICU admission	68	12	4
Fetal death	6	0	0
Neonatal death	8	2	0
Severe neonatal morbidity	22	2	2
Perinatal death	12	0	0

The proportion of preterm deliveries (100.0 %, 22.0 %, and 8.0 % in the EOP, LOP and no preeclampsia groups, respectively, $p < 0.0001$) and cesarean sections (90.0 %, 48.0 %, and 8.0 %, respectively, $p < 0.0001$) were significantly higher in both the EOP and LOP groups than in controls. Mean gestational age at delivery were earlier in the EOP group than in the LOP group ($p < 0.05$). Rates of SGA, were significantly elevated among mothers

with PE (32.0 %, 16.0 %, and 6.0 % in the EOP, LOP and no preeclampsia groups, respectively, $p < 0.0001$) and were more strongly associated with EOP (32.0 % vs 16.0 % in the EOP vs LOP groups, $p < 0.004$). The proportion of V. Apgar scores below 7 at 1 and 5 min were higher and neonatal birthweight was less in the EOP group than in LOP and control group.

The rates of all adverse birth outcomes, were higher among women with EOP. For example, the rates of fetal (3.0 % vs 0.0 %), neonatal (4.0 % vs 1.0 %), and perinatal death (6.0 % vs 0.0 %) were significantly higher in the EOP group than in LOP group ($p < 0.05$).

The rates of NICU admission (68.0 % vs 12.0 %, $p < 0.0001$) and severe neonatal morbidity (22.0 % vs 2.0 %, $p < 0.0001$) were significantly higher among the infants born to mothers with EOP.

Although the causes of preeclampsia are unclear, both maternal and placental factors contribute to the pathogenesis of this disease.

EOP is characterized by the inadequate and incomplete trophoblast invasion, abnormal placentation and spiral artery remodeling, tissue hypoxia in the placenta and fetus, the absence of compensatory mechanisms, and increased endothelial dysfunction factors. Early PE starts prior to week 34; it makes the most severe clinical manifestations, is associated with SGA, intrauterine growth restriction, abnormal blood circulation, early induced premature delivery, impossibility of prolonged pregnancy maintenance. On the contrary, late PE has a maternal etiology and is associated largely with somatic history. It develops after 34 weeks, has more favorable prognosis and the possibility of a more extended pregnancy prolongation.

Our study shows that effect of risk factors such nulliparity, chronic hypertension, and diabetes varies according to the subtype of preeclampsia. For example, women, who were young (younger than 20), nulliparous, had diabetes mellitus were significantly associated with increased risk of LOP, whereas women who had chronic hypertension, congenital anomalies had higher rates of EOP. Several risk factors were associated with preeclampsia, without a significant difference for early and late-onset disease. Maternal age more than 35 years, pregestational BMI more than 25 kg/m^2, smoking during pregnancy were significantly associated with increased risk of both EOP and LOP.

EOP had far greater adverse effects on the fetus and infant compared with LOP. We observed a stronger association between EOP and SGA (as compared with LOP and SGA). The rates of fetal, neonatal, and perinatal death, NICU admission, and severe neonatal morbidity were significantly higher in the EOP group than in LOP group.

Conclusions. Our research revealed that EOP is a distinct and a more severe clinical entity, associated with intrauterine growth restriction, high rates of adverse birth outcomes, a much earlier gestational age at onset and delivery. EOP starts with a failure to transform the maternal spiral arteries, subsequently followed by alterations of the villous trophoblast, and leads to severe placental lesion (early placental dysfunction), hypoxia of the placenta and fetus, the failure of compensatory mechanisms, an increase of endothelial dysfunction factors. Therefore, this subtype of preeclampsia debuted early (in midtrimester) and leads to worse perinatal outcomes. In comparison, LOP develops in the third trimester of pregnancy, rarely leads to perinatal loss. Our study confirms the heterogeneity of preeclampsia and shows that gestational age at the onset of the disease should be considered as an important indicator of disease severity and possibly of disease etiology.

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Introduction. Preeclampsia (PE) continues to be the leading cause of maternal and fetal morbidity and mortality worldwide with an incidence of 3.0-5.0 %. Recently evidence suggests that PE can be subdivided into early-onset PE (EOP), requiring delivery before 34 weeks' gestation and late-onset PE (LOP), with delivery at or after 34 weeks. They are associated with different maternal and fetal outcomes, biochemical markers, heritability, and clinical features. Although the diagnostic criteria are the same in each of these phenotypic variants of preeclampsia, they are characterized by different clinical features and are associated with different maternal and fetal outcomes. Within the context of personalized medicine, future lines for investigations dealing with the prediction and prevention of PE should be based on the identification of the PE subtypes with regard to the maternal characteristics and clinical factors.

Aim. The aim of this study was to study the incidence of early-onset and late-onset preeclampsia at a tertiary care center (at obstetrical department of L'viv Regional Clinical Hospital) and to find the difference in risk factors and birth outcomes associated with early-onset and late-onset preeclampsia.

Materials and methods. Clinical and anamnestic data were analyzed for 300 pregnant women aged 16-43 years old with singleton pregnancies divided into 3 groups: group I consisted of 100 patients with early-onset preeclampsia, group II-100 patients with late-onset preeclampsia; group III (control) consisted of 100 normotensive pregnant women who delivered consecutively after preeclamptic pregnant women. Preeclampsia was defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy. EOP was defined as onset of disease from 20 weeks 0 days to 33 weeks 6 days, whereas LOP was regarded as PE after 34 weeks' gestation.

Results. Our study shows that effect of risk factors such nulliparity, chronic hypertension, and diabetes varies according to the subtype of preeclampsia. For example, women who were young (younger than 20), nulliparous, had diabetes mellitus were significantly associated with the increased risk of LOP, whereas women who had chronic hypertension, congenital anomalies had higher rates of EOP. Several risk factors were associated with preeclampsia, without a significant difference for early and late-onset disease. Maternal age more than 35 years, pregestational BMI more than 25, smoking during pregnancy were significantly associated with increased risk of both EOP and LOP. The rates of all adverse birth outcomes were higher among women with EOP. For example, the rates of fetal, neonatal and perinatal death were significantly higher in the EOP group than in LOP group. The rates of NICU admission and severe neonatal morbidity were significantly higher among the infants born to mothers with EOP.

Conclusions. Our research revealed that EOP is a distinct and more severe clinical entity, associated with intrauterine growth restriction, with high rates of adverse birth outcomes, with a much earlier gestational age at onset and delivery. EOP starts with a failure to transform the maternal spiral arteries, subsequently followed by alterations of the villous trophoblast, lead to severe placental lesion (early placental dysfunction), hypoxia of the placenta and fetus, the failure of compensatory mechanisms, an increase endothelial dysfunction markers. Therefore, this subtype of preeclampsia debuted early (in the midtrimester) and leads to worse perinatal outcomes. In comparison, LOP develops in the third trimester of pregnancy, rarely leads to perinatal loss.

Keywords: preeclampsia, early onset of preeclampsia, late onset of preeclampsia, risk factors, birth outcomes.

Рання і пізня прееклампсія: різні чинники ризику та перинатальні наслідки

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Вступ. Прееклампсія (ПЕ) – основна причина материнської і перинатальної захворюваності й смертності. За останні десятиріччя розширилися уявлення про гетерогенну природу ПЕ. Згідно з сучасними дослідженнями, ПЕ може виявлятись у двох фенотипічних варіантах: із ранньою (до 34 тижнів вагітності) та пізньою (після 34 тижнів вагітності) маніфестацією. Хоча діагностичні критерії однакові в кожному з цих варіантів, вони характеризуються різними клінічними ознаками, мають різні перинатальні наслідки та ускладнення материнського організму. В межах концепції персоналізованої медицини майбутні напрями досліджень прогнозування та профілактики ПЕ мають ґрунтуватися на виявленні й уточненні підтипів ПЕ з урахуванням материнських характеристик та клінічного перебігу вагітності.

Мета. Визначення частоти ПЕ з ранньою (до 34 тижнів вагітності) та пізньою (після 34 тижнів вагітності) маніфестацією у пацієнток пологового відділення Львівської обласної клінічної лікарні й аналіз чинників ризику та перинатальних наслідків, характерних для різних підтипів ПЕ.

Матеріали й методи. У дослідження включено 300 вагітних віком 16–43 роки з одноплідною вагітністю. Їх було поділено на три ґрупи: вагітні з раннім початком прееклампсії, вагітні з пізнім початком прееклампсії та контрольна ґрупа. Діаґноз прееклампсії ставили відповідно до критеріїв International Society for the Study of Hypertension in Pregnancy. Маніфестацію ознак прееклампсії від 20 тижнів 0 днів до 33 тижнів 6 днів визначали як ранній початок прееклампсії, пізнім початком вважали появу характерних симптомів після 34 тижнів вагітності.

Результати. Виявлено, що такі чинники ризику, як вік понад 35 років, преґестаційний індекс маси тіла більше 25, куріння під час вагітності суттєво збільшують ризик виникнення прееклампсії. Деякі чинники ризику – перша вагітність, артеріальна ґіпертензія, цукровий діабет – мають виражену асоціацію з певними підтипами ПЕ. Наприклад, пізній початок ПЕ характерний для молодих жінок (віком до 20 років) з першою вагітністю, а також вагітних із цукровим діабетом, тоді як, пацієнтки із артеріальною ґіпертензію, природженими аномаліями розвитку плода мали більш високий ризик виникнення раннього початку ПЕ.

Негативні перинатальні наслідки частіше спостерігались у ґрупі з раннім початком ПЕ. Так, показники антенатальної, неонатальної та перинатальної смертності були значно вищими у ґрупі з раннім початком ПЕ, ніж у ґрупі із пізнім початком ПЕ.

Частота шпиталізації у відділення реанімації новонароджених і важкої захворюваності новонароджених була значно вищою у дітей, народжених матерями з ранньою маніфестацією ПЕ.

Висновки. Рання прееклампсія – найважчий клінічний варіант перебігу захворювання, який асоціюється із затримкою росту плода, часто завершується індукованими передчасними пологами і призводить до ґірших перинатальних наслідків. Виникнення ранньої прееклампсії може бути зумовлене порушенням інвазії трофобласта, незавершеною трансформацією спіральних артерій, а також раннім виникненням дисфункції плаценти, що призводить до ґіпоксії тканин плаценти і плода, відсутності компенсаторних механізмів, посилення ендотеліальної дисфункції. Цей підтип прееклампсії дебютує рано (в II – на початку III триместру) і призводить до ґірших перинатальних наслідків. Пізня прееклампсія виникає у III триместрі вагітності й рідко спричинює перинатальні втрати.

Ключові слова: прееклампсія, рання прееклампсія, пізня прееклампсія, чинники ризику, перинатальні наслідки.