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Delayed versus early delivery leads to similar outcome in selected cases of preeclampsia in the Finnish Genetics of Pre-eclampsia Consortium (FINNPEC) cohort

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ABSTRACT

Objectives: Most guidelines recommend induction of labor after 37 weeks of gestation in preeclampsia. This study assessed the effect of interval between diagnosis of preeclampsia and delivery on maternal and perinatal outcomes.

Study design: A cohort of 1637 women with preeclampsia recruited at five university hospitals in Finland was studied. Outcomes were compared in two groups according to the time interval between diagnosis of PE and delivery: delivery in less than 10 days (the early delivery group) and delivery at 10 days or later after the diagnosis (the delayed delivery group).

Main outcome measures: Maternal outcomes included significantly preterm delivery (delivery before 34 weeks of gestation), placental abruption, eclampsia and maternal intensive care or intensive monitoring for more than 24 h. Neonatal outcomes included small for gestational age, Apgar score of less than seven at the age of five minutes, umbilical artery pH < 7.05 and fetal death.

Results: No differences in frequency of preterm deliveries or maternal need for intensive care were observed between groups. Eclampsia and fetal death were rare, and their incidence did not differ between the groups. No maternal deaths were observed. Low Apgar score at five minutes of age was reported more commonly in the early delivery group, but there was no difference in fetal acidemia between groups.

Conclusion: Early and delayed delivery lead to comparable outcomes in this cohort. Expectant management could be beneficial in women with an unripe cervix or preterm preeclampsia without severe features.

1. Introduction

Preeclampsia (PE) is a complex vascular pregnancy disorder that is associated with morbidity and mortality for both the mother and the infant. It is a multisystem disorder and can lead to adverse outcomes such as maternal stroke, renal and hepatic injury, and fetal growth restriction. [1] PE is characterized by hypertension and proteinuria manifesting after the 20th weeks of gestation, or, in the absence of proteinuria, impaired organ function or uteroplacental dysfunction [2].

There is no cure for PE, but the symptoms usually begin to resolve soon after delivery. Most current guidelines recommend induction of labor after 37 weeks of gestation. In late preterm PE, planned delivery

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has been shown to reduce maternal morbidity but no greater neonatal morbidity [3] The optimal time depends on the wellbeing and possible complications of the mother and the infant.

The aim of this study was to assess the effect of interval between diagnosis of PE and delivery on maternal and perinatal characteristics and short-term outcomes in a cohort recruited from all university hospitals in Finland. This retrospective study represents the clinical standard care in the Finnish university hospitals during the recruitment period. We hypothesized that delaying the delivery would predispose patients to more severe morbidity, as PE has been considered a progressive disease that will not resolve until delivery of the placenta.

2. Methods

This study was conducted using data from the Finnish Genetic of Preeclampsia Consortium (FINNPEC) cohort. Details of the cohort have been published elsewhere [2]. In short, the study participants were recruited from the five university hospitals in Finland during 2008–2011. Eligible were both nulliparous and multiparous women with singleton pregnancies. Exclusion criteria included maternal age < 18 years and multiple pregnancy. Clinical data on pregnancy and delivery were collected from the medical records, from the Medical Birth Registry and from the Finnish Care Register for Health Care (HILMO). The original cohort description included 1450 PE women. Here we also included additional 187 FINNPEC participants whose data were processed later.

PE was defined by hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) and proteinuria (urinary excretion of protein ≥ 0.3 g in 24 h or 0.3 g/L, or two ≥ 1 + readings on a dipstick during random urine determination without an evidence of a urinary tract infection [4]. Superimposed PE was defined as development of new onset proteinuria in a woman with hypertension before 20 weeks of gestation. The HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) was diagnosed if two or more of the following criteria were met: ALAT (alanine aminotransferase) ≥ 70 U/L, ASAT (aspartate aminotransferase) ≥ 70 U/L, platelets ≤ 100 E9/L, lactate dehydrogenase ≥ 235 U/L. Eclampsia was defined as a new-onset tonic-clonic seizure in women with PE [4].

Time from diagnosis to delivery was compared in two groups: delivery in less than 10 days after the diagnosis of PE (the early delivery group) and delivery at 10 days or later after the diagnosis (the delayed delivery group). Furthermore, subgroup analyses were made in women who delivered preterm (<37 weeks of gestation), women with early onset PE (delivery < 34 weeks of gestation), women suffering from superimposed PE, and women who had the HELLP syndrome, and women who received the diagnosis of PE at full term.

Maternal pregnancy outcomes included early or moderately preterm delivery (before 34 weeks of gestation), placental abruption, eclampsia, or maternal intensive care or intensive monitoring for more than 24 h. Neonatal outcomes included small for gestational age (SGA, defined as birth weight below −2.0 SD according to Finnish standards [5], Apgar score at the age of five minute < 7, umbilical artery pH < 7.05 and fetal death.

2.1. Statistical analyses

Analyses were performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). The Mann-Whitney *U* test, chi-squared test and Fisher's exact test were used as appropriate. A p-value < 0.05 was considered statistically significant. All p-values are two-tailed.

3. Results

Women in the early delivery group were diagnosed with PE at later gestation and delivered at slightly later gestation compared to women in the delayed delivery group. Median highest blood pressure values were slightly lower but abnormalities in blood tests more profound (median highest ALAT values higher and lowest platelet values lower) in the early delivery group compared to the delayed delivery group.

No difference between the two groups was observed in frequency of cesarean delivery or in the frequency of delivery before 34 weeks of gestation. Although eclampsia occurred predominantly and maternal intensive care was needed slightly more often in the early delivery group, these differences between the groups did not reach statistical significance. A tendency of lower incidence of placental abruptions was observed in the early delivery group compared to the delayed delivery group, but the incidences were low, and the difference was not statistically significant. Neonatal depression (Apgar score < 7 at the age of five minutes) was more common in the early delivery group than in the delayed delivery group, but the frequency of fetal acidosis was similar in the two groups. Table 1 describes details of the main analyses.

Patient records of eclamptic women were reviewed to find explanatory factors. In the early delivery group, four women had eclampsia during labor and six during the post-partum period. Only two women had eclampsia before delivery: the other was diagnosed with early-onset PE nine days before delivery and had begun responding to multi-drug antihypertensive treatment, and the other one was diagnosed with late-onset PE on the same day eclampsia occurred. In the delayed delivery group, all three eclampsia cases occurred during delivery. Two of

Table 1
All preeclampsia.

Characteristics	Delivery in less than 10 days after diagnosis n = 955		Delivery in 10 days after diagnosis or later n = 682		*p* value
	n or median	% or min, max	n or median	% or min, max	
Primiparous	723	75.7	492	72.1	0.104
Maternal age at delivery	30	18, 45	30	18, 47	0.041
Gestational age at diagnosis, weeks + days	37 + 1	22 + 5, 41 + 6	35 + 1	23 + 0, 40 + 1	<0.001
Gestational age at delivery, weeks + days	37 + 5	23 + 0, 42 + 0	37 + 5	25 + 5, 41 + 6	0.009
Time from diagnosis to delivery, days	4	0, 9	16	10, 72	<0.001
Highest systolic BP in pregnancy, mmHg	165	118, 239	169	133, 230	0.002
Highest diastolic BP in pregnancy, mmHg	110	90, 173	110	88, 137	<0.001
Highest ALAT (U/l)	30	6, 1822	23	7, 2018	0.008
Lowest platelets (E9/l)	168	22, 408	184	44, 366	<0.001
Highest uric acid (μmol/l)	379	189, 680	375	165, 620	0.466
Maternal outcomes					
Cesarean section	477	49.9	339	49.8	0.947
Delivery before 34 weeks of gestation	186	19.5	127	18.6	0.665
Placental abruption	7	0.8	10	1.6	0.171
missing data	121		65		
Eclampsia	12	1.3	3	0.4	0.087
antepartum	2				
intrapartum	4				
postpartum	6		3		
Maternal intensive care*	49	5.6	25	4.0	0.150
Neonatal outcomes					
SGA	205	21.5	164	24.0	0.218
Apgar 5 min < 7	52	9.0	22	5.4	0.033
missing data	376		272		
Umbilical artery pH < 7.05	17	2.0	10	1.6	0.579
missing data	104		59		
Fetal death	2	0.2	0		0.514**

*Or intensive monitoring for more than 24 h, **Fisher's exact.

these were diagnosed during active labor and without preceding severe symptoms, and the remaining one during a complicated elective cesarean delivery.

3.1. Subgroup analyses

In women who delivered preterm, results were similar with main analyses. The only exception was gestational age at delivery. Trends in the highest blood pressure values and laboratory test abnormalities were similar with main analyses but statistically not significant, as were variables describing maternal and neonatal outcomes. Cesarean delivery was very common in the women who delivered preterm. See Table 2 for details of the preterm deliveries. See Table 2 for details of deliveries before 37 completed gestational weeks and Table S1 for deliveries before 34 completed gestational weeks.

Analyses of women with superimposed PE also showed similar trends to main analyses, although also in this subgroup gestational age at delivery was lower in the early delivery group. Eclampsia was not observed. Table 3 describes detailed data on these women.

Women with the HELLP syndrome had similar characteristics and outcomes as women in the main analyses. Only a minority of women needed intensive care, and no difference between the two groups was observed. Low Apgar score was less often observed in the early delivery group than in the delayed delivery group, but the difference was not statistically significant. See Table 4 for details.

In women who were diagnosed with PE at term, maternal and neonatal complications were rare and did not differ between the study groups. Only one placental abruption was reported (in the early delivery group), as well as five cases of eclampsia in the early delivery group (0.9 % of women) and two in the delayed delivery group (1.6 % of women, p = 0.628). Details are shown in Table S2.

Table 2
Delivery before 37 weeks of gestation.

Characteristics	Delivery in less than 10 days after diagnosis n = 359		Delivery in 10 days after diagnosis or later n = 273		*p* value
	n or median	% or min, max	n or median	% or min, max	
Primiparous	267	74.4	188	68.9	0.127
Maternal age at delivery	31	19, 44	30	18, 45	0.727
Gestational age at diagnosis, weeks + days	33 + 5	22 + 5, 36 + 6	32 + 0	23 + 0, 35 + 3	<0.001
Gestational age at delivery, weeks + days	34 + 2	23 + 0, 36 + 6	34 + 6	25 + 5, 36 + 6	0.027
Time from diagnosis to delivery, days	5	0, 9	14	10, 65	<0.001
Highest systolic BP in pregnancy, mmHg	175	132, 239	173	138, 225	0.517
Highest diastolic BP in pregnancy, mmHg	115	94, 173	112	97, 137	0.492
Highest ALAT (U/l)	49	8, 1822	34	10, 2018	0.002
Lowest platelets (E9/l)	158	22, 324	178	44, 366	0.002
Highest uric acid (μmol/l)	401	189, 579	355	198, 492	0.080
Maternal outcomes					
Cesarean section	285	79.4	202	74.0	0.110
Placental abruption	6	1.7	6	2.3	0.621
missing data	9		9		
Eclampsia	6	1.7	0		0.039**
Maternal intensive care*	31	9.4	18	7.0	0.311
Neonatal outcomes					
SGA	149	41.5	111	40.7	0.831
Apgar 5 min < 7	41	18.9	17	10.6	0.026
missing data	378		278		
Umbilical artery pH < 7.05	6	1.8	4	1.6	1.000**
missing data	30		19		
Fetal death	2	0.6	0		0.508**

*Or intensive monitoring for more than 24 h, ** Fisher's exact.
ALAT, alanine aminotransferase, SGA, small for gestational age (birth weight < -2 standard deviation), BP = blood pressure.

Table 3
Superimposed preeclampsia.

Characteristics	Delivery in less than 10 days after diagnosis n = 142		Delivery in 10 days after diagnosis or later n = 136		*p* value
	n or median	% or min, max	n or median	% or min, max	
Primiparous	94	66.2	83	61.0	0.370
Maternal age at delivery	32	19, 44	31	20, 45	0.707
Gestational age at diagnosis, weeks + days	35 + 3	25 + 0, 41 + 0	34 + 4	23 + 0, 39 + 3	0.004
Gestational age at delivery, weeks + days	35 + 6	25 + 6, 41 + 4	37 + 4	25 + 5, 41 + 5	0.018
Time from diagnosis to delivery, days	4	0, 9	18	10, 65	<0.001
Highest systolic BP in pregnancy, mmHg	177	128, 239	175	133, 225	0.299
Highest diastolic BP in pregnancy, mmHg	118	97, 173	114	94, 137	<0.001
Highest ALAT (U/l)	38	8, 885	23	8, 849	0.002
Lowest platelets (E9/l)	186	44, 355	210	49, 366	0.040
Highest uric acid (μmol/l)	408	189, 547	372	167, 529	0.133
Maternal outcomes					
Cesarean section	97	68.3	74	54.4	0.017
Delivery before 34 weeks of gestation	46	32.4	32	23.5	0.100
Placental abruption	2	1.4	4	3.1	0.430**
missing data	1		7		
Eclampsia	0		0		
Maternal intensive care*	13	9.6	6	4.5	0.103
Neonatal outcomes					
SGA	41	28.9	33	24.3	0.385
Apgar 5 min < 7	13	13.8	2	2.2	0.004
missing data	48		45		
Umbilical artery pH < 7.05	2	1.7	1	0.8	0.616**
missing data	21		10		
Fetal death	1	0.7	0		1.000**

*Or intensive monitoring for more than 24 h, ** Fisher's exact.
ALAT, alanine aminotransferase, SGA, small for gestational age (birth weight < -2 standard deviation), BP = blood pressure.

4. Discussion

In this study of 1637 women in the FINNPEC cohort diagnosed with PE we compared the association of interval between diagnosis and delivery (less than 10 days in the early delivery group and at least 10 days in the delayed late delivery group) with maternal and perinatal adverse outcomes. Eclampsia, fetal death, and placental abruption were rare and observed mainly in the early delivery group. No maternal deaths occurred in the cohort. The rate of maternal intensive care unit admission was not increased in the delayed delivery group and was relatively rare even in the HELLP syndrome subgroup. Apgar scores at the age of five minutes were lower in the early delivery group with the exception in the HELLP subgroup, but rates of fetal acidosis did not differ between the two groups.

A randomized study by Chappell et al [3] concluded that initiation of

Table 4
The HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome.

Characteristics	Delivery in less than 10 days after diagnosis n = 93		Delivery in 10 days after diagnosis or later n = 33		*p* value
	n or median	% or min, max	n or median	% or min, max	
Primiparous	79	84.9	28	84.8	0.989
Maternal age at delivery	30	19, 40	33	26, 45	0.178
Gestational age at diagnosis, weeks + days	34 + 5	22 + 5, 41 + 6	32 + 6	23 + 0, 37 + 4	0.011
Gestational age at delivery, weeks + days	35 + 4	23 + 0, 42 + 0	36 + 0	25 + 5, 39 + 5	0.518
Time from diagnosis to delivery, days	3	0, 9	18	10, 65	<0.001
Highest systolic BP in pregnancy, mmHg	174	139, 224	183	151, 230	0.122
Highest diastolic BP in pregnancy, mmHg	112	92, 140	113	103, 131	0.178
Highest ALAT (U/l)	198	37, 1822	165	49, 2018	0.769
Lowest platelets (E9/l)	90	22, 280	105	44, 222	0.042
Highest uric acid (μmol/l)	357	272, 524	347	303, 390	0.497
Maternal outcomes					
Cesarean section	67	72.0	25	75.8	0.680
Delivery before 34 weeks of gestation	32	34.4	10	30.3	0.667
Placental abruption	1	1.1	1	3.1	0.451**
missing data	1		1		
Eclampsia	7	7.5	0		0.105
antepartum	1				
intrapartum	2				
postpartum	4				
Maternal intensive care*	11	12.4	4	12.9	0.937
Neonatal outcomes					
SGA	33	35.5	10	30.3	0.590
Apgar 5 min < 7	6	12.5	5	22.7	0.275
missing data	45		11		
Umbilical artery pH < 7.05	3	3.3	0		0.566**
missing data	3		1		
Fetal death	0		0		

*Or intensive monitoring for more than 24 h, **Fisher's exact.
ALAT, alanine aminotransferase, SGA, small for gestational age (birth weight < -2 standard deviation), BP = blood pressure.

delivery soon after diagnosis reduces maternal morbidity compared to expectant management in late preterm PE, a finding repeated by a large *meta*-analysis [6]. The cost of reduced maternal morbidity is an increase in neonatal morbidity, which prompted the authors of another *meta*-analysis to conclude that delaying induction of labor may be feasible in some cases [7]. As strong conclusions cannot be drawn due to cohort design and smaller numbers in this study. In this study women with more severe features of PE were probably more likely managed more actively (as evidenced by lower gestational age at diagnosis in subgroup analyses and laboratory abnormalities in all analyses). A retrospective study design inherently places more severe cases into the early delivery group, biasing the results in favor of the delayed delivery group. However, our data suggests that in the FINNPEC cohort, expectant management did not lead to impaired outcome, not even at full term. As term PE often progresses to PE with severe features [8], close monitoring and facilities to perform urgent delivery are warranted, as evidenced by the unpredictable cases of eclampsia during delivery.

National guidelines [9] have suggested that women with HELLP syndrome should give birth as soon as they are diagnosed regardless of the weeks of gestation. Our data challenges this view, as a quarter of women with HELLP syndrome were delivered more than ten days after the diagnosis with comparable outcomes. However, caution is needed in this population, as the syndrome has been consistently linked with severe maternal and fetal morbidity and mortality[10], and in our study the number are small.

Diagnostic criteria of PE have become broader, resulting in increased incidence of the disease, but it has been speculated whether identifying women earlier or with milder phenotypes leads to improved outcomes [11]. On the other hand, organ dysfunction has been associated with more severe phenotype than proteinuria alone [12]. Finnish Current Care Guidelines on hypertensive pregnancy and pre-eclampsia (published in 2021) suggest delaying delivery until 37 weeks of gestation to avoid neonatal complications, unless maternal or fetal well-being can't be confirmed [13]. Participants in the FINNPEC study cohort were recruited before the national guidelines were available. Our data suggests that both maternal and neonatal complications due to cesarean deliveries and iatrogenic preterm births may have been avoided by clinical decision-making regarding timing of delivery.

Based on the details of eclamptic women, it seems that eclampsia is a rare but insidious complication not always presenting with warning signs, as noted also by Bartal and Sibai [14]. Although effective management of hypertension and expedited delivery are key points in managing PE, midwives and obstetricians should be prepared to recognize and treat eclampsia promptly.

The strength of this study was its detailed data from the cohort. Also, the FINNPEC jury protocol, which consisted of preeclampsia professionals assessing the exact moment of diagnosis, ensured exact timing of diagnoses and deliveries. Time of the diagnosis does not equal the exact time of disease onset, but this is the case also in clinical situations, where decisions have to be made based on the information available.

The weakness of our study is the nonrandomized design as well as the small number of women in the superimposed PE and the HELLP syndrome groups, and fortunately, low incidence of severe complications. The data were collected exclusively from the university hospitals, and it is possible that the cohort represents more PE with severe features. However, although these hospitals serve as tertiary centers, they are also responsible for secondary maternity care as well as all deliveries in the area. Furthermore, it could be expected that this would bias the results towards supporting a more active management. Because some of the neonatal outcome data was registry-based (Apgar scores and umbilical pH values), some data was missing. The most severe complications of PE are still quite rare, and a much larger sample size would be needed to evaluate these outcomes.

Large studies advocating active management after the diagnosis of PE [6], as well as this study, compare only short term maternal and neonatal outcomes. The complex long-term effects of SGA, early term delivery and maternal PE itself remain to be solved [15].

Although national guidelines have been published rather recently, our data shows that clinicians have managed PE pregnancies recommending delivery when more severe features are observed. Based on our study, delivery may be delayed in selected cases. This could be beneficial for example in women with unripe cervix so as to avoid unnecessary caesarean section and, most importantly, to avoid unnecessary prematurity and neonatal morbidity.

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6. Author's contributions

KK, JU, and HL designed the research. KK, EK, and HL collected the data. KK, ET, AK, EK, JU, and HL contributed to the data analysis. All authors read and approved the final manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The authors confirm that some access restrictions apply to the data. The researchers interested in using the data must obtain approval from the FINNPEC Board (steering committee). The researchers using the data are required to follow the terms of several clauses designed to ensure the protection of privacy and compliance with relevant Finnish laws. Data requests may be subject to further review by the Ethics Committee and may also be subject to individual participant consent.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2024.101129.

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