의학석사학위논문

Higher rate of Epstein-Barr virus incorporation on decidualendometrial cells in pregnant women with preeclampsia

자간전증 산모의 태반 내막세포에서 엡스타인-바 바이러스 감염 세포의 증가에 대한 분자병리학적 연구

2018년 2월

서울대학교대학원
의학과산부인과학전공
김혜성

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지도 교수 박중 신

이 논문을 의학석사 학위논문으로 제출함

2017년 12월

서울대학교 대학원

의학과 산부인과학 전공

김 혜 성

김혜성의 의학석사 학위논문을 인준함

2017년 12월

위 원 장 김 한 석 (인)

부위원장 박 중 신 (인)

위 원 박 찬 욱 (인)

Abstract

Introduction: There are various theories regarding the pathogenesis and pathophysiology of preeclampsia, but the exact cause of preeclampsia is not yet clearly established. Previous investigators have suggested that preeclampsia may be associated with Epstein-Barr virus (EBV) infection in the B lymphocytes during pregnancy based on polymerase chain reaction or serological tests. The purpose of this study was to evaluate the prevalence of EBV-positivity in women diagnosed with and without preeclampsia using placental specimens.

Materials and methods: This retrospective study included 85 pregnant women with preeclampsia and 65 pregnant women without preeclampsia. Placental specimens were assessed for the presence of acute and chronic inflammation. EBV-positivity was evaluated using in situ hybridization on EBV genes from tissue microarray slides. Clinicopathological characteristics were compared between women with and without preeclampsia and between EBV-positive and EBV-negative women.

Results: Women with preeclampsia showed a higher occurrence of EBV-positive cells than those without preeclampsia (36.5% vs 20.0%, p = 0.028). When stratified into gestational age, the occurrence of EBV-positivecells were consistently higher in women with preeclampsia with preterm delivery (39.1% vs 20.0%, p = 0.042) but not in those

with full-term (28.6% vs 20.0%, p = 0.497).

Conclusion: We found increased EBV infected placenta of women with preeclampsia compared with those without preeclamplasia. Further study is needed to elucidate the etiological role of EBV infection during development of preeclampsia.

Keywords: Preeclampsia, Epstein-Barr virus; in situ hybridization; virus latency; endometrial

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Abbreviations:

ACOG = American College of Obstetricians and Gynecologists

BMI = body-mass index

DBP = diastolic blood pressure

DNP = dinitrophenyl

EBV = Epstein-Barr virus

FFPE = Formalin-fixed and paraffin-embedded

HELLP = hemolysis, elevated liver enzyme levels, and low platelet levels

HRP = horseradish peroxidase

ISH = In situ hybridization

PCR = polymerase chain reaction

SBP = systolic blood pressure

TMA = tissue microarray

INTRODUCTION

Preeclampsia is one of the leading causes of maternal and fetal morbidity and mortality, including preterm delivery (1). Given its prevalence of approximately 5-8% among pregnancies, it is considered to be a serious risk (2). Preeclampsia is clinically diagnosed when new-onset hypertension with proteinuria or new-onset hypertension occurs with any one of the following: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual problems after 20 weeks of gestation (3). As of now, there are various theories regarding the pathogenesis and pathophysiology of preeclampsia, such as abnormal placentation leading to hypoxic placenta, maternal endothelial dysfunction, increased systemic inflammatory response, and immunological,hormonal, nutritional, or angiogenic factors—however, the exact cause of preeclampsia is not yet clearly established (4).

A few investigators reported that EBV infection may be associated with several pathologic conditions during pregnancy such as stillbirth, depression, and preeclampsia (5-7). In those studies, their association was mostly thought to be associated with EBV infection of the B lymphocytes based on polymerase chain reaction (PCR) or serological tests with blood samples, but not histopathological specimens. In addition, the possibility of vertical transmission of EBV during pregnancy through the placenta has been suggested, but the infected cells have not been well characterized (8). Recently, Kim et al reported that EBV-infected cells were present in the endometrial glandular epithelial cells in the placenta(9). Therefore, the purpose of this study was to evaluate the prevalence of

EBV-positivity in women diagnosed with and without preeclampsia using histopathological specimens of the placenta.

MATERIALS AND METHODS

Patient population

Pregnant women giving birth in Seoul National University Hospital during 2005 to 2016 were the subjects of this study. This case-control study was approved by the Institutional Review Board of Seoul National University Hospital (reference No. H-1704-151-848). We searched the preeclampsia patients using our electronic medical records and selected the patients with available placenta specimens at the Department of Pathology.

Eighty-five patients who developed preeclampsia were matched for maternal age within 10 years, and gestational age at delivery within 3 weeks with 65 controls with normal outcomes (ratio approximately 1:1).We excluded the pregnant women with multiple gestation, chronic hypertension, or systemic lupus erythematosus.

Clinical information

Clinicopathological data including maternal age, gestational age, gravity, parity, height, pre- and post-pregnancy body-mass index (BMI), proteinuria, blood pressure, history of labor induction, placental weight, fetal death, fetal weight, fetal gender, and Apgar scores were obtained from the electronic medical records.

Preeclampsia was diagnosed when hypertension (systolic blood pressure [SBP] higher than 140 mmHg or diastolic blood pressure [DBP] higher than 90 mmHg on at least two occasions of 4 hours apart) presented after 20 weeks of gestation combined with

proteinuria (> 300 mg/24 h or random proteinuria ≥ [+]), or other maternal organ dysfunction such as liver involvement, neurological or hematological complications, renal insufficiency according to the American College of Obstetricians and Gynecologists (ACOG) guidelines (10).

We classified preeclampsia into mild and severe. Severe preeclampsia was defined when one or more of symptoms or signs below was present: severe headache, visual disturbance, epigastric pain, eclampsia, severe hypertension (SBP/DBP above 160/110 mmHg),hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) syndrome. Patients with preeclampsia not meeting the criteria above were categorized as having mild preeclampsia.

Placental tissues

Formalin-fixed and paraffin-embedded (FFPE) placental tissues were analyzed Histopathologic examination was done to evaluate the acute and chronic inflammatory status of placenta. Specifically, we assessed for the presence of acute chorioamnionitis, acute funisitis, chronic villitis, chronic chorioamnionitis, and chronic deciduitis(11). Acute inflammation was considered present when either acute chorioamnionitis or acute funisitis was observed, while chronic inflammation was defined as the presence of any of chronic villitis, chronic chorioamnioitis, or chronic deciduitis. Several cores of 2.0 mm in diameter were selected from each placenta and re-arranged into tissue array blocks.

mRNA ISH by RNAscope

In situ hybridization (ISH) was performed with RNAscope FFPE assay kit (Advanced Cell Diagnostics, Inc., Hayward, CA, USA) according to the manufacturer's instruction. The probes of the genes for in situ hybridization includes four latent genes; EBV-encoded RNA-1 (EBER), EBV nuclear antigen-1 (EBNA1), late membrane antigen (LMP1), and BamH1-a rightward transcript (RPMS1). In brief, 4-μm TMA sections were heated and digested for pretreatment. The sections were hybridized with each probe that target four different latent genes. Each target probe contains a 25-base region complementary to the target RNA, a spacer sequence, and a 14-base tail sequence, called Z probe. A pair of target probes (double Z probes), each possessing a different type of tail sequence, hybridize contiguously to a target region (50 bases). The two tail sequences together form a 28-base hybridization site for the preamplifier, which contains 20 binding sites for the amplifier that, in turn, contains 20 binding sites for the label probe. Thereafter, a HRP-based signal amplification system was applied to target probe before color development with 3,3'-diaminobenzidine. Detailed information of the probes is described in the previous publication(9). Positive staining was defined as brown dots or clusters within the boundary of the cellular membrane including nucleus and cytoplasm. The housekeeping gene ubiquitin C served as a positive control for intact mRNA. The DapB gene, encoding Bacillus subtilis dihydrodipicolinate reductase, was used as a negative control.

Statistical analysis

All statistical analyses were performed using SPSS (version 21.0.0, IBM Corp., Armonk, NY, USA). The correlation between disease status (with or without preeclampsia) or EBV-positivity and clinicopathological variables were determined using the chi-square test, Fisher's exact test, or Student's t-test, as appropriate. For variables that were significantly different, further subgroup analysis was performed stratified to gestation age (i.e., preterm [<37 weeks] and full-term [≥37 weeks] delivery) and severity preeclampsia (i.e., patients without preeclampsia, with mild preeclampsia, and with severe preeclampsia). Results were considered statistically significant when p values were less than 0.05.

RESULTS

Comparison of clinicopathologic characteristics between women with and without preeclampsia

A total of 150 women (85 and 65 with and withoutpreeclampsia, respectively) and their placentas were investigated. With regard to disease severity among the women with preeclampsia, there were 30 and 55 patients with mild and severe preeclampsia, respectively. The clinicopathologic characteristics of women with and without preeclampsia are shown in Table 1. The mean gestational age of the women with preeclampsia (33.4 years ± 4.4) was not significantly different from that of women without preeclampsia (34.6 ± 3.7, p = 0.061). A history of full-term delivery was significantly higher in women without preeclampsia (15.3% vs 41.5% in women with and without preeclampsia, respectively, p <0.001), whereas that of preterm delivery was significant greater in women with preeclampsia (22.4% vs 4.6%, p = 0.002). Fetal weight was significantly lower in women with preeclampsia (1.8 kg vs 2.3 kg, p = 0.001), especially in women with preterm delivery (1.5 kg vs 1.9 kg, p = 0.006), but not those with full-term delivery (p = 0.064). Placental weight was significantly smaller in women with preeclampsia (414.5 g vs 550.8 g, p <0.001). The Apgar scores at 1 minute were significantly lower in women with preeclampsia (proportion of scores ≤7 of 75.3% vs 49.2%, p = 0.001), but Apgar scores at 5 minutes were not statistically significantly different between the two groups (27.7% vs 32.9%, p = 0.490). Acute inflammation was more frequently seen in the group without preeclampsia (29.4% vs 49.2%, p = 0.013) but

other pathologic characteristics including acute chorioamnionitis, acute funisitis, chronic villitis, chronic deciduitis, and chronic inflammation were not significantly different between the two groups (p = 0.079-0.972). (Fig. 1)

Occurrence of EBV(+) cells between preeclampsia and control patients

The in situ hybridization staining of the EBV showed that the positive signals are shown in the same cells in all four latent genes (EBER1, EBNA1, LMP1, and RPMS1), although the intensity varies slightly in four different genes (Fig. 2.). They were found only in the cells at the decidua near the chorioamniotic membranes, and positive cells were cuboidal with round to oval nuclei arranged in a single layer which surrounded the dilated lumina containing secretory materials. These EBV positive cells were proved to be the glandular endometrial cells in our previous paper using immunohistochemical staining methods (JKMS, in press).

Table 2 shows that EBV infection rate in decidua was significantly different between women with and without preeclampsia. Women with preeclampsia showed a higher occurrence of EBV-positive cells (36.5% vs 20.0%, p = 0.028). When stratified into gestational age, the occurrence of EBV-positive cells were even higher in women with preeclampsia with preterm delivery (39.1% vs 20.0%, p = 0.042).

Table 3 demonstrates the comparison of clinicopathological features between EBV-positive and EBV-negative preeclampsia patients. Pre- and post-pregnancy BMI (kg/m^2)

were both significantly lower in the EBV-positive patients (21.0 vs 22.7, p = 0.040 in pre-pregnancy and 25.7 vs 27.4, p = 0.033 in post-pregnancy). On the other hand, other characters (i.e., maternal age, gestational age at delivery, history of full-term or preterm delivery history, history of spontaneous or artificial abortion, maternal height, proteinuria, systolic and diastolic BP, fetal death, fetal weight, fetal gender, Apgar scores at 1 and 5 minutes, placental weight, acute chorioamnionitis, funisitis, inflammation and chronic villitis, chorioamnionitis, deciduitis, inflammation) were not significant different between EBV-positive and EBV-negative preeclampsia patients (p = 0.060-1.000). Although they did not show statistically significant difference, the EBV infection rate in severe preeclampsia patients (40%) was higher than that in mild preeclampsia patients (30%).

Table 1. Comparison of clinicopathological features between pregnant women with and without preeclampsia.

		Disease		
	Unit/ Category	Preeclampsia (%) (N=85)	Control (%) (N=65)	P value
Maternal age (mean ± SD)	Years	33.7 ± 4.7	33.7 ± 3.9	0.895
(range)		19-47	26-43	
Gestational age at delivery	Weeks	33.3 ± 4.4	34.6 ± 3.7	0.061
Full-term delivery history	Present	13 (15.3)	27 (41.5)	<0.001
Preterm delivery history	Present	19 (22.4)	3 (4.6)	0.002
Spontaneous abortion history	Present	16 (18.8)	10 (15.4)	0.581
Artificial abortion history	Present	12 (14.1)	8 (12.3)	0.747
Maternal height	cm	160.4 ± 5.2	161.7 ± 5.7	0.152
Pre-pregnancy BMI	kg/m^2	22.0 ± 3.6	21.95 ± 4.3	0.911
Post-pregnancy BMI	kg/m^2	26.8 ± 3.6	25.79 ± 4.7	0.156
Proteinuria	1+-4+	43 (50.6)	2 (3.1)	<0.001
Systolic BP	mmHg	162.3 ± 16.9	125.8 ± 15.8	<0.001
Diastolic BP	mmHg	105.2 ± 9.8	81.1 ± 11.3	<0.001
Fetal death	Dead	1 (1.2)	2 (3.1)	0.579*
Fetal weight	kg	1.8 ± 0.9	2.3 ± 0.9	0.001
<37 weeks		1.5 ± 0.7	1.9 ± 0.7	0.006
≥37 weeks		2.8 ± 0.4	3.1 ± 0.4	0.064
Fetal gender	Male	54 (63.5)	35 (53.8)	0.232
	Female	31 (36.5)	30 (46.2)	
Apgar score 1 min	≤7	64 (75.3)	32 (49.2)	0.001
Apgar score 5 min	≤7	18 (27.7)	28 (32.9)	0.490
Placental weight	g	414.5 ± 187.0	550.8 ± 181.4	<0.001
Acute chorioamnionitis		0 (0.0)	3 (4.6)	0.079*
Acute funisitis		1 (1.2)	5 (7.7)	0.085*
Acute inflammation		25 (29.4)	32 (49.2)	0.013
Chronic villitis		9 (10.6)	7 (10.8)	0.972
Chronic chorioamnionitis		22 (25.9)	17 (26.2)	0.970
Chronic deciduitis		16 (18.8)	10 (15.4)	0.581
Chronic inflammation		32 (37.6)	24 (36.9)	0.928

Note—Continuous variables were compared using Student's t test and categorical variables with Chi-square test except for otherwise specified.
* Comparison done using Fisher exact test

Table 2. No. of placentas with EBV-positive cells in the decidua in pregnant women with and without preeclampsia. EBV-positive cells are more frequently encountered in preeclampsia than control patients, especially in cases with gestational age less than 37 weeks.

	Disease		P value
	Preeclampsia (%)	Control (%)	
Total cases	(N=85)	(N=65)	0.028
EBV(+) cells in decidua present	31 (36.5)	13 (20.0)	
Gestational age less than 37 weeks	(N=64)	(N=40)	0.042
EBV(+) cells in decidua present	25 (39.1)	8 (20.0)	
Gestational age 37 weeks or older	(N=21)	(N=25)	0.497
EBV(+) cells in decidua present	6 (28.6)	5 (20.0))	

Table 3. Comparison of clinicopathological features between EBV-positive and EBV-negative status in preeclampsia patients.

	Unit/ Category	EBV status		P value
		EBV(+) (%) (N=31)	EBV(-) (%) (N=54)	
Maternal age (mean ± SD) (range)	Years	33.2 ± 3.5 25-41	34.0 ± 5.3 19-47	0.398
Gestational age at delivery	Weeks	32.1 ± 5.5	34.0 ± 3.6	0.060
Full-term delivery history	Present	5 (16.1)	8 (14.8)	1.000 *
Preterm delivery history	Present	10 (32.3)	9 (16.7)	0.097
Spontaneous abortion history	Present	9 (29.0)	7 (13.0)	0.068
Artificial abortion history	Present	2 (6.5)	10 (18.5)	0.196 *
Maternal height	cm	160.5 ± 4.8	160.3 ± 5.5	0.836
Pre-pregnancy BMI	kg/m^2	21.0 ± 3.3	22.7 ± 3.7	0.040
<37 weeks		20.9 ± 3.2	22.5 ± 3.8	0.060
≥37 weeks		23.7 ± 5.8	21.5 ± 3.8	0.145
Post-pregnancy BMI	kg/m^2	25.7 ± 3.4	27.4 ± 3.6	0.033
<37 weeks		25.4 ± 3.8	26.3 ± 3.9	0.246
≥37 weeks		28.6 ± 4.6	26.7 ± 4.5	0.218
Proteinuria	1+-4+	17 (54.8)	26 (48.1)	0.553
Systolic BP	mmHg	161.7 ± 12.9	162.7 ± 18.9	0.786
Diastolic BP	mmHg	107.5 ± 8.5	103.8 ± 10.4	0.098
Fetal death	Dead	1 (3.2)	0 (0.0)	0.365 *
Fetal weight	kg	1.6 ± 0.9	1.9 ± 0.9	0.171
Fetal gender	Male	21 (67.7)	33 (61.1)	0.541
	Female	10 (32.3)	21 (38.9)	
Apgar score 1 min	≤7	24 (77.4)	40 (74.1)	0.731
Apgar score 5 min	≤7	12 (38.7)	16 (29.6)	0.391
Placental weight	g	384.2 ± 170.6	431.9 ± 195.2	0.260
Acute chorioamnionitis		31 (100.0)	54 (100.0)	N/A
Acute funisitis		0 (0.0)	1 (1.9)	1.000 *
Acute inflammation		10 (32.3)	15 (27.8)	0.663
Chronic villitis		3 (9.7)	6 (11.1)	1.000 *
Chronic chorioamnionitis		9 (29.0)	13 (24.1)	0.615
Chronic deciduitis		6 (19.4)	10 (18.5)	0.924
Chronic inflammation		15 (48.4)	17 (31.5)	0.122
Preeclampsia severity	Mild	9 (30.0)	21 (70.0)	0.360
	Severe	22 (40.0)	33 (60.0)	

Note—Continuous variables were compared using Student's t test and categorical variables with Chi-square test except for otherwise specified.
* Comparison done using Fisher exact test
N/A = non-available

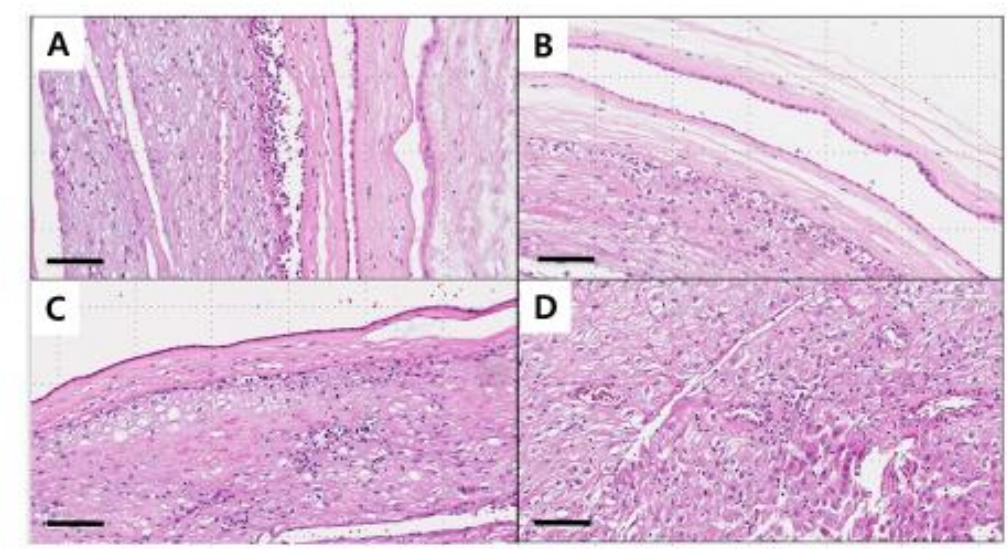

Fig. 1. Histologic features of placental inflammation. A, acute chrioamnionitis; B, chronic chorioamnionitis; C, chronic chorioamnionitis; D: chronic deciduitis. Scale bar = 50 μm (Original magnification X 200)

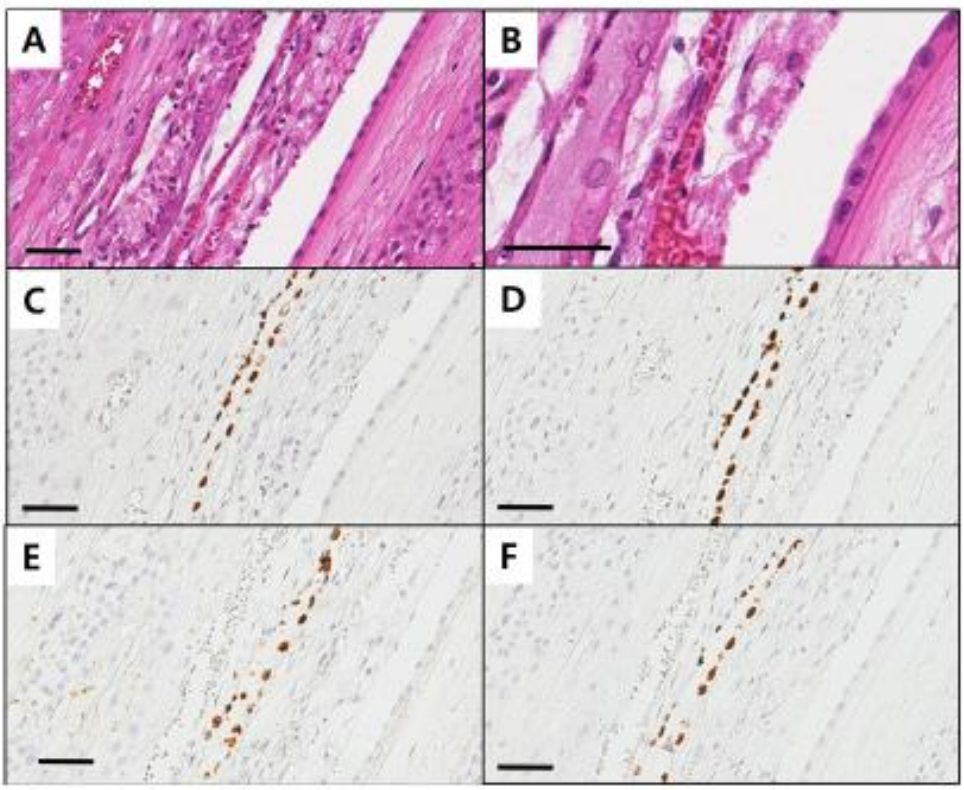

Fig. 2. Histologic and molecular features of EBV-positive cells. A, hematoxylin-eosin staining; B, high power view of hematoxylin-eosin staining; C, ISH of EBER1 gene; D, ISH of EBNA1 gene; E, ISH of LMP1 gene; F, ISH of RPMS1 gene. Scale bar = 50 μm (A,C,D,E,F: Original magnification X 200, B: X 400)

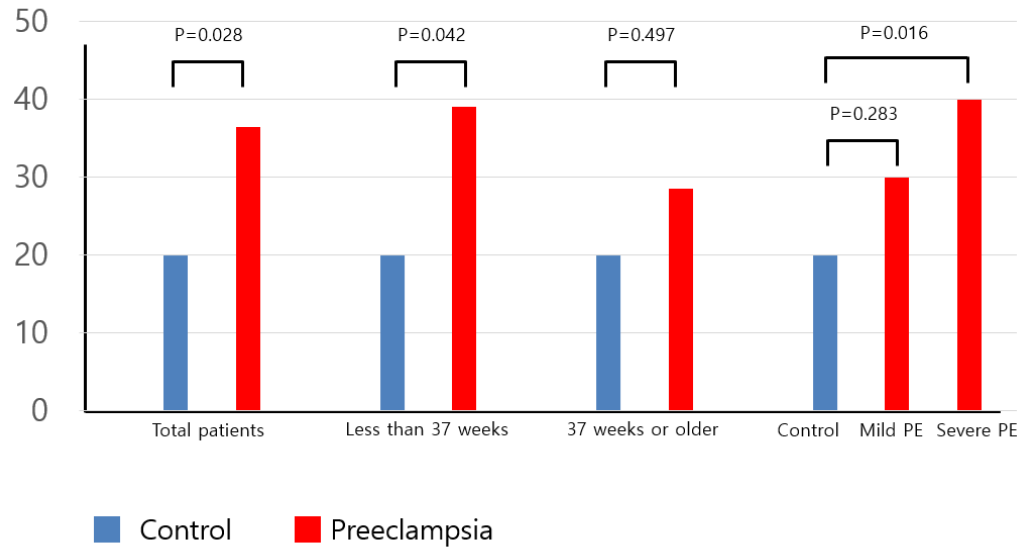

Fig. 3. Positive rate of EBV in control and preeclampsia.

DISCUSSION

In the present study, we observed the higher rate of EBV latent infection in pregnant women with preeclampsia compared with those without preeclampsia. The EBV-positive rate was higher in women withpreeclampsia than those withoutin the subgroup of women with gestational age 36 weeks or younger. To our knowledge, this is the first study to demonstrate the relationship between EBV infection and preeclampsia based on histopathological studies using tissue microarray and in situ hybridization on EBV genes. The results of our study corroborate previous studies in which (1) Kim et al (9) demonstrated that EBV-infected cells were present in the endometrial glandular epithelial cells in the placenta for the first time, (2) Prins et al (12) showed that decidual Epstein-Barr virus-induced gene 3 (EBI3) expression was higher in women with preeclampsia, (3) Elliott et al (7) observed increased antibody binding activity to epitopes from EBNA-1 and GPR50 among women with preeclampsia.

There are many hypotheses with regard to the relationship between EBV infection and preeclampsia. In the study of Kim et al (9), they presumed that EBV infection in the placenta was due to its immune tolerance, which is known to be expressing immune modulating programmed cell death ligand 1 (PD-L1) protein. Prins et al (12)found the increased EBI3 (Epstein-Barr virus induced 3) gene expression in placental mononuclear cells of preeclampsia patients. EBI3 is a

subunit of immune modulatory cytokines interleukin 27 (IL-27) and IL-35, and therefore related to the activated maternal immune state cytotoxic character of preeclampsia. However, they did not suggest any etiological role of EBV for the development of preeclampsia.

Elliot et al (7) found the increased antibody titer to EBNA1 gene in the serum of preeclampsia patients compared to control pregnant women. IgG aganist EBNA1 target the GPR50 due to molecular mimicry, and binding of IgG class of antibody to GPR50 produces the complement activation and complement deposition in the placenta, which can induce the preeclampsia in the EBV infected placenta.

Toll-like receptor (TLR) 3 may play an important role in the relationship between EBV and preeclampsia. Preeclampsia is known to be associated with innate immunity dysfunction which may be triggered by invading microorganisms (13). One previous study has linked TLR expression to the development of preeclampsia (14). TLR3 expressions is increased in placenta or immune cells in women with preeclampsia (15). The TLRs can be activated during cellular damage due to poor placentation, oxidative stress, and endothelial dysfunction. EBV activates TLR3 resulting in high type I interferon production and contribute to the innate and adaptive immune regulation.

Another theory considers oxidative stress to be an important component.

Preeclamspia is thought to be caused by poor placentation leading to placental ischemia (16). Placental ischemia leads to oxidative stress in the placenta and leads to shedding of syncytiotrophoblast debris into the maternal circulation making a systemic maternal inflammatory response and causing maternal vascular endothelial dysfunction (17). In a study with EBV-infected cell line, oxidative stress was produced after EBV lytic cycle induction (18). Significant increases of the reactive oxygen radical species (ROS) including BZLF-1, superoxide dismutase, and catalase gene expressions were observed during the induction of the EBV lytic cycle.

Clinicopathological features were compared between EBV-positive and EBV-negative women who were had preeclampsia. Among several variables, both pre- and post-pregnancy BMI were significantly lower in the EBV-positive patients compared with EBV-negative women while there were no significant difference in the other clinicopathological characteristics.

In the comparison of preeclamspia and control groups, acute inflammation of placenta was more frequently seen in the group without preeclampsia (29.4% vs 49.2%, $p = 0.013$). We speculate that the difference might be attributed to the unusual characteristic of the control groupin our hospital. In the control group, 61.5% (40/65) of the patients had delivered before 37 weeks, which was due to the following reasons: preterm premature rupture of membrane (n = 14), preterm

labor (n = 11), placenta previa bleeding (n = 5), fetal growth restriction (n = 4), fetal anomaly (n = 4), fetal death in utero (n = 1), and maternal breast cancer (n = 1). Majority was preterm premature rupture of membrane and preterm delivery, which contributed to more than half of preterm control group. As preterm premature rupture of membrane and preterm delivery is known to be associated with infection and inflammation, this may have been why the group without preeclampia demonstrated a significantly higher rate of acute inflammation on placenta specimens (19).

The major strength of our study is the large study population (N = 150), compared to the relatively small study population of previous studies showing the relationship between preeclampsia and EBV (7, 12). This large number of study was possible due to the specific method used in our study (i.e., tissue microarray), which enabled us to investigate large number of samples with small number of slides. On the other hand, a limitation of this study is that the measurement of EBV antibodies in patients' serum was not performed.

In conclusion, we found that increased occurrence of EBV-positive cells was more frequent in women with preeclampsia compared with those without preeclamplasia. Based on the findings of this study, EBV infection in the placenta may be one of the etiological factors of preeclampsia. Further study is needed whether EBV infection plays any role during the development of preeclampsia or

not.

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자간전증 산모의 태반 내막세포에서 엡스타인-바 바이러스 감염 세포의 증가에 대한 분자병리학적 연구

한글초록

서론:자간전증의 병인 및 병리 생리학에 관한 다양한 이론이 있지만 자간전증의 정확한 원인은 아직 명확하게 밝혀지지 않았다. 이전 연구자들은 자간전증이 임신 중 B림프구의 엡스타인바 바이러스 (EBV) 감염과 관련이 있다고 보고하였으나, 이 연구들은 중합 효소 연쇄 반응 (PCR)이나 혈청 검사를 기반으로 한 연구들이었다. 따라서, 이 연구의 목적은 태반 조직을 이용하여 자간전증으로 진단된 산모와 그렇지 않은 산모에서의 EBV 양성률을 분석하고자 한다.

방법: 이 후향적 연구는 자간전증이있는 산모 85명과 자간전증이 없는 임신부 65명을 대상으로 하였다. 태반 표본에 대하여 급성 및 만성 염증의 유무를

평가 하였다. EBV 양성 유무는 조직 미세배열 (tissue microarray) 슬라이드에서 EBV 유전자에 대한 인 사이투하이브리드형성법 (in situ hybridization)을 사용하여 평가하였다. 자간전증이 있는 산모와 그렇지 않은 산모 간에, 그리고 EBV (+) 와 EBV (-) 여성간에 임상병리학 적 특성을 비교하였다.

결과:자간전증이있는 여성은 자간전증이없는 여성보다 EBV(+) 세포의 발생 빈도가 높았다 (36.5% vs 20.0%, p = 0.028). 재태 연령으로 계층화 한 경우, 조산한 자간전증 여성에서 EBV (+) 세포의 발생 빈도가 높았으나 (39.1% vs 20.0%, p = 0.042) 만삭 분만한 여성에서는 그렇지 않았다 (28.6% vs 20.0%, p = 0.497).

결론:자간전증이 없는 여성에 비해 자간전증이 있는 여성에서 EBV에 감염된 태반의 빈도가 높다는 것을 발견했다. 자간전증 발생 기전 가운데 EBV 감염의 병인학적인 역할을 밝히기 위해서는 추가적인 연구가 필요하다.

2017-21928

김혜성