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RISK FACTORS, CLINICAL ASPECTS, AND *FOKI* POLYMORPHISM OF VITAMIN D RECEPTOR GENE IN PREECLAMPSIA CASES ATTENDING COMBINED MILITARY HOSPITAL, MUZAFFARABAD, AZAD KASHMIR

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Preeclampsia (PE) is a pregnancy-related disorder. The current research was performed to study the epidemiology, clinical characteristics and predictive role of reproductive and demographic risk factors in the development of preeclampsia (PE). Furthermore, a *FOKI* sequence variant of *VDR* gene (rs2228570) was analyzed to see its association with pre-eclampsia phenotype.Current case-control study comprising of PE patients and age-matched controls recruited from the Gynecology department of Combined Military Hospital (CMH), Muzaffarabad, Azad Kashmir was conducted from August 2021 to January 2022 at Quaid-i-Azam University Islamabad, Pakistan. A predesigned questionnaire was used to collect socio-demographic information, clinical parameters, reproductive health, family history of hypertension, and various lifestyle factors from PE patients and controls. SPSS 20 was used to analyze the data. Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (RFLP-PCR) method was executed on extracted DNA samples of PE patients to examine the genotypes for *VDR FOKI*

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polymorphism. Out of 1933 pregnant women who delivered at CMH, Muzaffarabad during April to July, 2021, 3.10% were diagnosed with PE. A total of 300 pregnant females were recruited for this case control study out of which 60 were PE patients and 240 were age matched controls. SPSS analysis of data showed that family history of hypertension and previous miscarriage history were strongly associated with high risk of PE ($p<0.05$), whereas multiparity and proper supplements intake during pregnancy were strongly associated with decreased risk of PE in AJK women ($p<0.05$). Clinical characteristics i.e., Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Alkaline Phosphatase (ALP), Alanine Transaminase (ALT) and urinary proteins were found significantly elevated while blood haemoglobin was significantly lower in PE patients ($p<0.0001$). Frequency of minor allele of *FOKI* polymorphism was higher in PE patients but no significant association was detected. PE had a frequency of 3.10% among pregnant females presented at CMH, Muzaffarabad. Identification of positive association of family history of hypertension, previous miscarriage history with PE onset and high frequency of *FOKI* minor allele in PE patients reaffirms their involvement in PE etiology.

Key words: Pre-eclampsia, risk factor analysis, miscarriage, hypertension, *FOKI* polymorphism, *VDR* gene

INTRODUCTION

Preeclampsia (PE) is a pregnancy specific disorder that results in a maternal and perinatal morbidity as well as mortality in severe cases. In developing countries, PE is a serious pregnancy complication which later becomes a reason of maternal mortality as PE along with seizures leads to eclampsia which account for more than 12% of maternal mortality (MIR *et al.* 2019). PE is also a major cause of perinatal deaths, intrauterine growth restrictions, maternal morbidity, and preterm births (SIBAI *et al.* 2005; SHAMSI *et al.* 2013). Annually about 500,000 fetal or infant and 76,000 worldwide maternal fatalities are caused by preeclampsia (DULEY 2009; KHOWAJA *et al.* 2016). The prevalence of preeclampsia and eclampsia was about 19 percent in Pakistan, where 1 in 89 pregnant women dies of the pregnancy complication (SHAMSI *et al.* 2010; NASEEB *et al.* 2015). According to previous studies, various risk factors play a role in the development of PE, as PE's pathogenesis is multifactorial, caused by both genetic and non genetic risk factors (GEORGE *et al.* 2010; GANNOUN *et al.* 2015). Furthermore, impaired placentation is also thought to be linked with the development of PE (GEORGE *et al.* 2010). Studies reported that Vitamin D may have a role in the pathogenesis of preeclampsia by altering blood pressure through calcium homeostasis and/or modifying inflammation and immunology (CACCAMO *et al.* 2020; FARAJIAN-MASHHADI *et al.* 2020). In addition, researchers discovered an inverse relationship between plasma 1, 25 (OH)2-D3 levels and blood pressure (PURSWANI *et al.* 2017).

Vitamin D Receptor (VDR) is found not only in the traditional target organs, i.e., bone, kidney, and skin, but also in the decidua and placenta, where vitamin D may affect foetal growth as well as pregnancy (PURSWANI *et al.* 2017; REZAVAND *et al.* 2019). Furthermore, several epidemiologic studies have shown that vitamin D deficiency is linked to an increased risk of PE (ROBINSON *et al.* 2010; WEI *et al.* 2013), and that it may affect the onset of PE by increasing inflammation and/or causing a lack of immunosuppression (SHIN *et al.* 2010). In the *VDR* gene,

single-nucleotide polymorphisms are common. The four most common *VDR* gene diallelic polymorphisms: BsmI (A>G, rs1544410) and ApaI (A>C, rs7975232) on the final intron, and *FOKI* (C>T, rs2228570) and TaqI (T>C, rs731236) on the coding exons have been studied frequently for their association with hypertension and PE (KNABL *et al.* 2017; REZAVAND *et al.* 2019).

Non-genetic risk factors for PE have been reported in many studies from various populations, including Sierra Leone, the Netherland, England, New Mexico, the United Kingdom, the United States of America (SILVA *et al.* 2008; PARÉ *et al.* 2014; BARTSCH *et al.* 2016; STITTERICH *et al.* 2021), but there are few such reports from Pakistan (SHAMSI *et al.* 2010) and none of them is based on the population of Azad Jammu and Kashmir (AJK). Studies about PE risk factors identified parity, history of miscarriage, low supplement consumption during pregnancy, high body mass index, infertility treatment, pre-existing hypertension, pre-gestational diabetes, male fetus, very low birth weight, previous PIH history, gestational diabetes, and a family history of hypertension as potential contributors (SHAMSI *et al.* 2010; LISONKOVA *et al.* 2013; ENGLISH *et al.* 2015; QUAN *et al.* 2018; YOU *et al.* 2018).

PE contributors in the AJK population may differ from those previously reported for other populations because of variances in socioeconomic features, lifestyle, education, and possible exposure to risk factors. PE-related maternal as well as fetal mortality is highest in developing nations, such as Pakistan, and is ascribed to late diagnosis due to a lack of awareness and access to early screening as well as management (NORWITZ *et al.* 2009; BHUTTA *et al.* 2013). Therefore, identifying PE risk factors in the local population from various regions can aid in awareness, early diagnosis, and in time management to avoid adverse outcomes. Therefore, the current study was planned to examine epidemiology, clinical characteristics, and non-genetic risk factors related to PE as well as the *FOKI* polymorphism for its contributing role in PE development in AJK women.

MATERIALS AND METHODS

For this case-control study, 60 PE patients and 240 age-matched controls out of a total 1933 pregnant females visiting the Gynae Department of Combined Military Hospital (CMH), Muzaffarabad, were recruited from April 2021 to July 2021. The study was approved by the Bio-Ethical Review Committee of Quaid-i-Azam University, Islamabad, and also permission was granted from the Department of Medical Education of CMH Muzaffarabad, AJK. The sample size was calculated using Epitools software by considering a 5% margin of error with the hazard ratio 2, and a power of 80% (SERGEANT 2018).

The sampling was done by a non-probability consecutive sampling method. Patients with confirmed preeclampsia having systolic blood pressure (SBP) $\geq$ 140 mmHg, or diastolic blood pressure (DBP) $\geq$ 90 mmHg with protein loss of $\geq$300 mg in 24-hour urine specimen (proteinuria) who visited the hospital during study period were taken as cases, regardless of age, family history, clinical presentation, or other factors. Healthy pregnant women with no history of preeclampsia and matched in age to the PE cases were taken as controls for this study. Informed consent was signed by both the PE patients and the controls.

A predesigned questionnaire was used to collect the data. The questionnaire was organized using information from previously published reports. It was translated into the local language as needed and then back into English to verify data consistency and correctness. The

data was collected on socio-demographic, anthropometric such as blood group, BMI, infant sex and infant weight, clinical and reproductive characteristics, as well as family history of hypertension in first and second degree relatives, various lifestyle factors such as education, occupation, consanguinity, smoking and various medical related risk factors such as preexisting hypertension, pre-gestational diabetes, fertility treatment, deceased child history, neonatal morbidity, previous fetal complications and supplement intake during pregnancy etc. by a structured questionnaire. Body mass index (BMI) was calculated using height and weight data collected for each participant, and the results were classified using World Health Organization (WHO) cut-off values for Asian countries (KHAN *et al.* 2017) (Figure 1).

SPSS 20 was used to analyze the data of non-genetic risk factors and clinical parameters. Continuous variables were reported as mean ± standard deviation (SD), whereas qualitative variables were expressed in terms of frequencies and percentages. Independent sample t-test was used to compare the clinical parameters of cases and controls. To identify the possible risk factors linked with PE, the cox regression model was used. The odds ratios (ORs) obtained were utilized to evaluate the contribution of each factor. 95% confidence interval (CI) was determined for all ORs and $P<0.05$ was considered statistically significant.

For the molecular analysis only 40 patients agreed to participate with confirmed preeclampsia were considered as cases in this study. Their blood samples were collected in EDTA coated tubes and stored at -4˚C. DNA of each collected blood sample was extracted by phenol-chloroform method. Extracted DNA was used to amplify the exon 2 of *VDR* gene by polymerase chain reaction (PCR) using forward (5′CTGGCACTGACTCTGGCTC3′) and reverse primer (5′ATGGAAACACCTTGCTTCTTCTCCCTC3′). A restriction fragment length polymorphism (RFLP) technique was used to confirm the *FOKI* minor allele rs2228570 (T>C) in the collected samples. *FOKI* fast digest restriction enzyme (Thermo Fisher Scientific Company) was used which cuts a wild-type sequence (ATG) into two bands of sizes 197 and 62bp. However, if the target sequence contains T>C polymorphism with ACG variant instead of ATG, the enzyme does not cleave, and a single band is obtained on agarose gel. PCR products after restriction enzyme digestion were loaded on a 2.5% agarose gel, and genotypes were predicted based on bands shown under UV light in a gel documentation system (Figure 1).

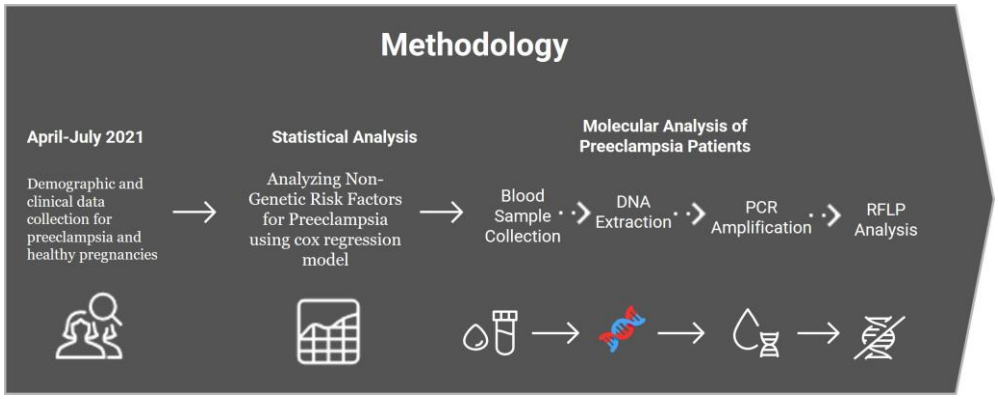

Figure 1. Summary scheme of methodology used in this study

RESULTS

Of the 300 pregnant women recruited for this study, 60 and 240 were cases and controls respectively. Baseline characteristics of cases and controls are enlisted in table 1 (Table 1).

Table 1. Baseline Characteristics of PE patients and Controls

Baseline Characteristics		Cases		Controls	
		Frequency	Percentage	Frequency	Percentage
Age	≤ 21	6	10.0	24	10.0
	22-29	26	43.3	104	43.3
	30-37	23	38.3	92	38.3
	≥ 38	5	8.3	20	8.3
Age at Marriage	≤ 20	28	46.7	101	42.1
	21-28	28	46.7	123	51.3
	≥ 29	4	6.7	16	6.7
Gestational Age (weeks)	≤ 30	10	16.7	4	1.7
	31-38	48	80.0	193	80.4
	≥ 39	2	3.3	43	17.9
Education	Uneducated	17	28.3	59	24.6
	Primary	9	15.0	51	21.3
	Secondary	17	28.3	70	29.2
	Higher Education	17	28.3	60	25.0
Occupation	Student	1	1.7	7	2.9
	Housewife	46	76.7	207	86.3
	Working	13	21.7	26	10.8
Cousin Marriage	Yes	34	56.7	138	57.5
	No	26	43.3	102	42.5
Parity	Primiparity	21	35.0	58	24.2
	Multiparity	20	33.3	107	44.6
	Grandparity	19	31.7	75	31.3
Miscarriage	No	37	61.7	164	68.3
	1-2	16	26.7	69	28.8
	Many(3-5)	7	11.7	7	2.9
Infertility Treatment	Yes	8	13.3	19	7.9
	No	52	86.7	221	92.1
Patient Smoking	Yes	2	3.3	2	.8
	No	58	96.7	238	99.2
Blood Group	N/A	12	20.0	21	8.8
	A positive	10	16.7	60	25.0
	A negative	1	1.7	4	1.7
	B positive	6	10.0	65	27.1
	B negative	0	0	6	2.5
	O positive	27	45.0	62	25.8
	O negative	2	3.3	6	2.5
	AB positive	2	3.3	16	6.7
Supplements Intake	Yes	45	75.0	205	85.4
	No	15	25.0	35	14.6
Singlets/Twins	Single	58	96.7	237	98.8
	Twins	2	3.3	3	1.3
Previous Fetal Complications	Yes	3	5.0	6	2.5
	No	57	95.0	234	97.5
Family History	Yes	45	75.0	43	17.9

	No	15	25.0	197	82.1
Current Delivery Mode	Cesarean	51	85.0	182	75.8
	Vaginal	9	15.0	58	24.2
Previous Mode of Delivery	No	21	35.0	70	29.2
	Cesarean	17	28.3	107	44.6
	Vaginal	22	36.7	63	26.3
BMI	<18.5	2	3.3	22	9.2
	18.5-24.9	15	25.0	109	45.4
	25-29.9	21	35.0	64	26.7
	>30	22	36.7	45	18.8
Stillbirth	Yes	8	13.3	5	2.1
	No	52	86.7	235	97.9
Infant Sex	N/A	1	1.7	1	.4
	Boy	27	45.0	119	49.6
	Girl	31	51.7	118	49.2
	Both Girls	0	0	2	0.8
	Both Boys	1	1.7	0	0
Infant Weight (kg)	N/A	20	33.3	9	3.8
	≤ 2	3	5.0	6	2.5
	2.1-3.5	36	60.0	202	84.2
	≥ 3.6	1	1.7	23	9.6
Neonatal Morbidity	Yes	5	8.3	8	3.3
	No	55	91.7	232	96.7
Geographic Distribution of Participants	Muzaffarabad	47	78.3	203	84.6
	Neelum Valley	3	5.0	10	4.2
	Bagh	2	3.3	11	4.6
	HattianBala	7	11.7	11	4.6
	Other	1	1.7	5	2.1
Deceased Child History	Yes	1	1.7	21	8.8
	No	59	98.3	219	91.3
GDM	Yes	10	16.7	20	8.3
	No	50	83.3	220	91.7
Chronic Hypertension	Yes	6	10.0	8	3.3
	No	54	90.0	232	96.7
Pregestational Diabetes	Yes	1	1.7	2	0.8
	No	59	98.3	238	99.2
Previous History of PIH	Yes	8	13.3	21	8.8
	No	52	86.7	219	91.3
Systolic Blood Pressure	Low	1	1.7	29	12.1
	Normal	1	1.7	160	66.7
	High	58	96.7	51	21.3
Diastolic Blood Pressure	Low	0	0	42	17.5
	Normal	2	3.3	164	68.3
	High	58	96.7	34	14.2
Platelets	Low	7	11.7	2	0.8
	Normal	50	83.3	236	98.3
	High	3	5.0	2	0.8
Alkaline Phosphatase (ALP)	Normal	18	30.0	234	97.5
	High	42	70.0	6	2.5
Alanine Transaminase (ALT)	Normal	35	58.3	239	99.6
	High	25	41.7	1	0.4

Serum Creatinine	Low	8	13.3	50	20.8
	Normal	37	61.7	190	79.2
	High	15	25.0	0	0
Serum Urea	Low	3	5.0	18	7.5
	Normal	44	73.3	212	88.3
	High	13	21.7	10	4.2
Urinary Protein	300(+)	8	13.3	240	100.0
	600(++)	30	50.0	0	0
	900(+++)	19	31.7	0	0
	> 900	3	5.0	0	0
Blood Hemoglobin	Low	41	68.3	81	33.8
	Normal	19	31.7	159	66.3
Serum Bilirubin	Normal	55	91.7	240	100.0
	High	5	8.3	0	0

Mean values of each continuous variable including age, gestational age at time of enrollment, age at marriage, BMI are shown in Table 2 for both cases and controls (Table 2). Average age for both cases and controls were same i.e. 29.23±5.94 years. Mean values of gestational age are respectively documented as 34.70±3.258 and 37.22±2.115 weeks in cases and controls, so cases were observed to have less gestational age at the time of childbirth. For cases and controls, average values for age at marriage were respectively observed as 21.93±3.973 and 21.99±3.893 years. Average values of the continuous variable e.g., BMI was 28.32±5.580kg/m^2 for cases and 25.03±5.844kg/m^2 for controls, which showed that PE patients had increased weight compared to controls. Mean values of infant weight were respectively found as 1.84±1.379 and 2.91±1.460 kg for cases and controls, which depicts that the infant weight of PE patients was low in comparison to controls.

Table 2. Mean values of continuous variable of PE patients and controls

Characteristics	Cases	Controls
Age± SD (years)	29.23±5.944	29.23±5.906
Gestational Age± SD (weeks)	34.70±3.258	37.22±2.115
Age At Marriage± SD (years)	21.93±3.973	21.99±3.893
BMI± SD (kg/m^2)	28.32±5.580	25.03±5.844
Infant Weight± SD (kg)	1.84±1.379	2.91±1.460

SD: standard deviation

Table 3 presents the comparative statistical analysis of clinical and pathological data of PE patients and controls (Table 3). The mean systolic blood pressure was 145.33±15.78 mmHg and 121.21±7.64 mmHg in cases and controls, respectively ($p<0.0001$). The mean diastolic blood pressure was 95.67±7.45 mmHg and 79.71±6.56 mmHg in cases and controls, respectively ($p<0.0001$). Average systolic and diastolic blood pressure in cases was found higher than the controls.

Mean blood hemoglobin (Hb) in cases was 11.16±1.55 g/dl and in controls it was 12.10±1.10 g/dl ($p<0.0001$) as enlisted in table 3 (Table 3). The mean value of blood Hb in cases was found lower than the controls. Mean platelet count in cases was 265.50±86.52 ($10^3/\mu L$) while in controls it was 286.87±62.30 ($10^3/\mu L$) ($p=0.03$). The average value of platelet count in cases was found to be relatively smaller than that of the controls. The average value of alkaline phosphatase was observed as 305.50±132.64 (IU/L) in cases and 138.52±81.36 (IU/L) in controls ($p<0.0001$). Mean value of alanine transaminase was observed as 38.88±29.41 (IU/L) and 23.82±16.54 (IU/L) in cases and controls respectively ($p<0.0001$). Mean value of alkaline phosphatase and alanine transaminase in cases was elevated in comparison to controls. Mean serum bilirubin was 12.03±3.55 μmol/L in cases and 9.56±3.61 μmol/L in controls ($p<0.0001$). Mean serum creatinine was 99.95±26.54 mmol/L and 89.38±15.77 mmol/L in cases and controls, respectively ($p<0.0001$). Average value of serum urea was 5.58±1.50 mmol/L in cases, while 4.83±1.39 mmol/L in controls ($p<0.0001$). In cases mean value of serum bilirubin, creatinine, and urea were relatively higher than in controls. Mean value of urinary proteins was observed as 734.83±458.19 mg/24hrs and 300.00±0.00 mg/24hrs in cases and controls, respectively ($p<0.0001$). The average value of urinary proteins was found elevated in PE patients than the controls.

Table 3. Clinical and pathological data of PE patients and controls

Clinical and Pathological Data	Cases N=60	Controls N=240	t-value	p-value	95% CI of the difference	
					Lower	Upper
Systolic Blood Pressure (mmHg)	145.33±15.78	121.21±7.64	17.049	<0.0001	21.34	26.91
Diastolic Blood Pressure (mmHg)	95.67±7.45	79.71±6.56	16.395	<0.0001	14.04	17.87
Blood Hemoglobin (g/dl)	11.16±1.55	12.10±1.10	-5.425	<0.0001	-1.28	-0.60
Platelets Count ($10^3/\mu L$)	265.50±86.52	286.87±62.30	-2.184	0.030	-40.62	-2.11
Alkaline Phosphatase (IU/L)	305.50±132.64	138.52±81.36	12.338	<0.0001	140.35	193.62
Alanine Transaminase (IU/L)	38.88±29.41	23.82±16.54	5.282	<0.0001	9.45	20.68
Serum Bilirubin (μmol/L)	12.03±3.55	9.56±3.61	4.76	<0.0001	1.45	3.49
Serum Creatinine(mmol/L)	99.95±26.54	89.38±15.77	3.977	<0.0001	5.34	15.80
Serum Urea (mmol/L)	5.58±1.50	4.83±1.39	3.682	<0.0001	0.35	1.154
Urinary Protein (mg/24hrs)	734.83±458.19	300.00±0.00	14.777	<0.0001	376.92	492.74

N: number of participants

Cox regression analysis showed that previous miscarriage history and family history of hypertension were strongly associated with high risk of PE ($p<0.05$)(OR=1.740 and 9.235 respectively, 95%Cl) in our study cohort. However, multiparity and proper supplement intake during pregnancy were strongly associated with decreased risk of PE in pregnant women ($p<0.05$)(OR=0.370 and 0.483, respectively, 95%CI) recruited for this study as shown in table 4 (Table 4).

Table 4. Analysis of different risk factors for preeclampsia onset by cox regression model

	Characteristics	Regression Coefficient(ß)	*P*-value	OR (Exp ß)	95% CI of expected B	
					Lower	Upper
Reproductive risk factors	Gestational Age ≤30 30-38 ≥39	-0.200	0.118^{NS}	0.819	0.637	1.052
	Parity Primiparity Multiparity Grandparity	-0.995	0.026**	0.370	0.154	0.886
	Miscarriage Yes No	0.554	0.022**	1.740	1.083	2.795
	Age At Marriage ≤ 20 21-28 ≥ 29	0.555	0.089^{NS}	1.742	0.918	3.304
Medical Related Risk Factors	Chronic Hypertension Yes No	0.140	0.822^{NS}	1.150	0.339	3.899
	History Of PIH Yes No	-0.190	0.691^{NS}	0.827	0.323	2.115
	Pre gestational Diabetes Yes No	0.730	0.519^{NS}	2.074	0.226	19.032
	Supplements Intake Yes No	-0.728	0.054*	0.483	0.229	1.018
	Fertility Treatment Yes No	0.138	0.782^{NS}	1.148	0.431	3.057
	Family History Yes No	2.223	< 0.0001***	9.235	4.523	18.858
	GDM in Previous Pregnancy Yes No	-0.307	0.522^{NS}	0.736	0.288	1.883
	Previous Fetal Complications Yes No	1.529	0.067^{NS}	4.612	0.899	23.671
	Stillbirth in Current Pregnancy Yes No	0.453	0.545^{NS}	1.573	0.363	6.829
	Deceased Child History Yes	-0.474	0.663^{NS}	0.622	0.074	5.246

	No					
	Neonatal Morbidity [a]	-0.071	0.932[NS]	0.932	0.182	4.757
	Yes No					
Lifestyle Risk Factors	Education	-0.184	0.304[NS]	0.832	0.585	1.182
	Uneducated Primary Secondary Higher Education					
	Occupation	0.329	0.482[NS]	1.390	0.555	3.483
	Student Housewife Working					
	Consanguinity	-0.366	0.249[NS]	0.693	0.372	1.293
	Yes No					
	Smoking during pregnancy	0.562	0.591[NS]	1.754	0.226	13.632
	Yes No					
Anthropometric Risk Factors	BMI	0.037	0.206[NS]	1.038	0.980	1.099
	<18.5 18.5-24.9 25-29.9 >30					
	Blood Group	0.010	0.885[NS]	1.011	0.877	1.165
	N/A A positive A negative B positive B negative O positive O negative AB positive					
	Infant Sex	0.144	0.603[NS]	1.155	0.672	1.986
	N/A Boy Girl Both Girls Both Boys					
	Infant Weight(kg)	-0.042	0.761[NS]	0.959	0.731	1.258
	N/A ≤ 2 2.1-3.5 ≥ 3.6					
	Singlets/Twins Fetus	-0.368	0.670[NS]	0.692	0.127	3.759
	Single Twins					

CI: confidence intervals,OR: odds ratio,[NS]: Non-Significant,*: Significant association,**: Highly Significant association,***: Very highly significant association,[a]: Includes any of the following: respiratory distress, dehydration, blood infection, premature fetus and aspired meconium.

PCR was performed on 40 collected samples of PE patients. In order to check *VDR FOKI* polymorphism (T>C), RFLP analysis was executed. 26 samples cleaved into two bands of 197 and 62 bp long consistent with the wild type i.e. TT, 6 samples showed heterozygosity (genotype TC) and produced three bands of 259, 197 and 62 bp long on agarose gel, while 8 samples were not cleaved by enzyme digestion showing homozygous CC genotype (Figure 2).

Figure 2 depicts the agarose gel picture of some selected PE cases after restriction digestion with the *FOKI* endonuclease. The DNA ladder in the first well and the undigested PCR product in the second well served as a control band to compare band sizes before and after restriction enzyme digestion. In Figure 2, amplified fragments of PE13, PE14, PE22, PE23, PE35, PE44, and PE49 were cleaved by restriction enzyme and showed two bands on gel of 197 and 62bp which were of wild type genotype (TT). PE2 and PE12 were cleaved by the enzyme and produced three bands of 259, 197 and 62 bp which represent heterozygosity with genotype TC. While, PE1 and PE8 were not digested by the enzyme due to presence of *FOKI* polymorphism in the restriction site of enzyme and showed only single band of 259bp on the agarose gel which represents genotype CC (Figure 2).

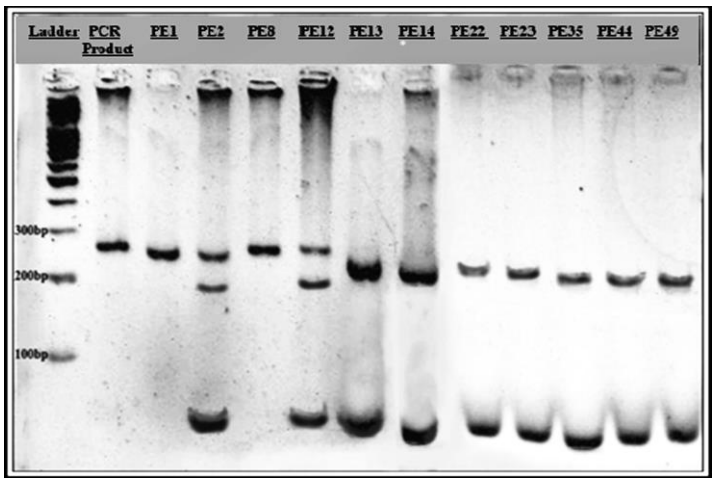

Figure 2. Agarose gel image after restriction digestion with *FokI* endonucleaseof some selected PE cases

A 2.5% agarose gel image showing PCR product after restriction digestion with *FOKI* endonuclease of some selected PE cases. Lane 1 represents the DNA ladder showing bands of different sizes and lane 2 represents the PCR product before restriction digestion with band size 259bp to see the difference in band sizes before and after restriction digestion. The *FOKI* endonuclease digested product of genotype CC homozygous PE cases appear on the gel with band size 259bp observed in lanes 3 and 5. Lane 7, 8, 9, 10, 11, 12, and 13 represents the wild type TT homozygous with the product size of 197bp and 62bp. Lane 4 and 6 represents the heterozygous TC with a product band size of 259bp, 197bp and 62 bp.

DISCUSSIONS

Preeclampsia is the most common disorder among pregnant women worldwide and is a major cause of perinatal deaths, intrauterine growth restrictions, maternal morbidity, and preterm birth (SIBAI *et al.* 2005; SHAMSI *et al.* 2013). Screening tools and preventive measures for PE are still lacking. Its treatment involves the management of adverse symptoms and fetal delivery,

which is the only ultimate cure (NORWITZ *et al.* 2009). Many previous studies have looked at the association between PE and other etiological factors (SILVA *et al.* 2008; SHAMSI *et al.* 2010; PARÉ *et al.* 2014; BARTSCH *et al.* 2016; STITTERICH *et al.* 2021). There has been no previous data on possible PE risk factors from the AJK population. However, geographical differences in PE incidence and mortality rates have been reported from different populations, so the current study was designed to explore epidemiology, clinical and reproductive characteristics, and potential PE risk factors in pregnant women from Muzaffarabad, AJK by using cox regression model.

Of the 60 preeclamptic patients, 6(10%) were aged ≤ 21 years, 26(43.3%) were aged 22-29 years, 23(38.3%) were aged 30-37 years and 5(8.3%) were aged ≥ 38 years. The majority of patients diagnosed with PE are between the ages of 22 and 29 with average age 29.23±5.944 years. Studies reported that women older than 35 years have 4-5 fold high risk of suffering from PE compared to women of 25-29 years age (LI *et al.* 2018; TYAS *et al.* 2019) whereas, in our study, most of the PE patients were 22-29 years old. This inconsistency might be due to the regional differences in the childbearing age of women and simply due to the fact there were more younger mothers than older mothers.

In this study, different clinical parameters of PE affected women were also analyzed. Out of which mean serum values of creatinine, bilirubin and urea were significantly raised in cases compared to controls ($p<0.0001$). These results are similar to the studies performed in Indian and Zimbabwe populations that reported an elevation in the average values of serum creatinine and urea in PE patients (MAKUYANA *et al.* 2002; MANJAREEKA *et al.* 2013; MONTEIRO *et al.* 2013; VYAKARANAM *et al.* 2015). Our findings were inconsistent with previous study by Müller-Deile *et al*. which found that blood creatinine and urea nitrogen levels in PE patients are similar to the levels found in non-pregnant female because of decreased renal plasma flow as well as glomerular filteration rate in PE patients, although normal pregnancy is characterized by increased renal plasma flow as well as glomerular filteration rate (MONTEIRO *et al.* 2013; MÜLLER-DEILE *et al.* 2014; VYAKARANAM *et al.* 2015). The elevation in the serum creatinine level might be due to reduce urinary clearance secondary to increased reabsorption and decreased glomerular filteration rate (JEYABALAN *et al.* 2007). Mean value of serum bilirubin was found significantly increased in cases than the controls that are consistent with the previous studies (MAKUYANA *et al.* 2002; MALVINO *et al.* 2005). A significant elevation ($p<0.0001$) of alkaline phosphatase (ALP), alanine transaminase (ALT), urinary protein, systolic blood pressure (SBP) and diastolic blood pressure (DBP) was observed in PE patients during this study. Similarly, many researchers also found significantly higher levels of ALP, ALT, urinary protein, systolic and diastolic blood pressure in patients which is consistent with our results (MAKUYANA *et al.* 2002; MALVINO *et al.* 2005; KURT *et al.* 2015; EKUN *et al.* 2018; LI *et al.* 2018).

In this study, significantly higher blood hemoglobin (Hb) ($p<0.0001$) and platelets count ($p<0.05$) were observed in controls as compared to PE patients but mean value of platelet count falls in a normal range. Our findings are consistent with studies of many previous researchers who found that mean values of blood Hb and platelet count were higher in normotensive controls compared to PE patients (KIRBAS *et al.* 2015; LI *et al.* 2018). Our finding is contradictory to Kurt *et al*. who reported that level of platelet count and blood Hb in PE patients and controls were similar (KURT *et al.* 2015).

Results of risk factors analysis by cox hazardous regression model showed that parity (*P*=0.026), history of miscarriage in patient with a single or more previous miscarriage (*P*=0.022), less supplements intake during pregnancy (*P*=0.054) and family history of hypertension (*P*<0.0001) were significantly associated with preeclampsia in this study. Among these risk factors multiparity and adequate intake of essential prenatal supplements during pregnancy especially folic acid and calcium were found to be responsible for decreasing the risk of PE (O.R<1, 95%CI) while history of miscarriage and family history of hypertension were found linked to increased risk (O.R>1, 95%Cl). Similar results were reported in many of the previous studies that reported primiparity, less intake of supplements during pregnancy and a family history of hypertension are significantly associated with the PE (SHAMSI *et al.* 2010; ENGLISH *et al.* 2015; YOU *et al.* 2018). The differences in results might be due to varied study area, small sample size and varied time duration of our study.

In our results, chronic hypertension, Body Mass Index (BMI), Gestational Diabetes Mellitus (GDM), history of diabetes mellitus, history of Pregnancy Induced Hypertension (PIH), infertility treatment, smoking during pregnancy, infant sex and weight showed no significant association (*P*>0.05) with PE risk. Several previous studies showed significant association between BMI, infertility treatment, preexisting hypertension, pregestational diabetes, male fetus, very low birth weight, previous PIH, GDM and risk of PE (LISONKOVA *et al.* 2013; LI *et al.* 2018; QUAN *et al.* 2018; YOU *et al.* 2018). However Lisonkova *et al*. reported that women who smoked during pregnancy had a lower risk of late onset PE (LISONKOVA *et al.* 2013).

VDR gene polymorphisms were reported to be linked with increased risk of PE (BODNAR *et al.* 2014; REZAVAND *et al.* 2019; CACCAMO *et al.* 2020; FARAJIAN-MASHHADI *et al.* 2020). BODNAR *et al*. reported that pregnant women with vitamin D deficiency were at increased risk of severe PE (BODNAR *et al.* 2014). To the best of knowledge, it is the first study of *VDR* polymorphisms among Kashmiri pregnant women affected with preeclampsia, as *VDR* polymorphisms were never studied in PE affected women from AJK and Pakistan.

In current study, we examined the sequence variant of initiation codon of exon 2 of *VDR* gene (*FOKI* polymorphism) in PE women for its contributing role. Minor allele 'C' of *FOKI* polymorphism of *VDR* gene was found in some of the PE patients. Rezavand *et al*. reported that *VDR FOKI* polymorphism was associated with 1.72- fold increased risk of PE (REZAVAND *et al.* 2019). *VDR FOKI* C allele changes the initiation codon ATG into ACG leading to a three amino acid short protein with enhanced biological activity (REZAVAND *et al.* 2019). For the transactivation of 1, 25-(OH)2- D3 signal, C allele of *VDR FOKI* polymorphism was found to be more effective in comparison to T allele (HUANG *et al.* 2006). However, SINGLA *et al*. reported that *VDR FOKI* polymorphism is associated with reduced risk of hypertension that showed inconsistency with our findings (SINGLA 2015). O'Callaghan *et al*. found the negative association between maternal 1, 25-(OH)2- D3 concentration and blood pressure as well as PE risk, but no association with the severity of PE (O'CALLAGHAN *et al.* 2018).

In this study, distribution of genotypes and alleles among cases was also observed. Minor allele frequency in PE patients was 27.5%. CACCAMO *et al*. found that *VDR* minor allele is associated with high blood pressure during pregnancy with two fold increased risk of gestational hypertension and 92% women with gestational hypertension that carries minor allele were found with insufficient vitamin D (CACCAMO *et al.* 2020). These findings suggest that *VDR FOKI*

polymorphism may influence the expression of *VDR* gene as well as the binding of 1, 25-(OH)2- D3 with *VDR* (NUNES *et al.* 2016). Summarizing our findings, it is suggested that there is a link between *FOKI* minor allele with PE onset as suggested in previous published reports but due to small sample size used for RFLP analysis and lack of data for controls we could not obtain statistically significant results.

CONCLUSIONS

There was significant association of family history of hypertension and previous miscarriage history with increased PE risk, whereas multiparity and proper supplements intake during pregnancy were strongly associated with decreased PE risk in AJK women. Clinical characteristics such as SBP, DBP, ALP, ALT and urinary proteins were found significantly elevated while blood Hb were significantly lower in PE patients. Our results will provide awareness regarding PE risk factors, which will pave the way for in time diagnosis and management to avoid adverse outcomes. Identification of *FOKI* minor allele in PE patients suggests its involvement in PE pathology in our study population. However, future large scale studies should be performed to get significant results regarding molecular markers including *FOKI*. Such studies will not only reveal early diagnostic markers but will provide awareness to women and their obstetric care providers to safeguard maternal and fetal health.

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FAKTORI RIZIKA, KLINIČKI ASPEKTI I FOKI POLIMORFIZAM GENA RECEPTORA VITAMINA D KOD PACIJENATA SA PREEKLAMPSIJOM U KOMBINOVANOJ VOJNOJ BOLNICI, MUZAFARABAD, AZAD KAŠMIR

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IZVOD

Preeklampsija (PE) je poremećaj povezan sa trudnoćom. Trenutno istraživanje je sprovedeno radi proučavanja epidemiologije, kliničkih karakteristika i prediktivne uloge reproduktivnih i demografskih faktora rizika u razvoju preeklampsije (PE). Analizirana je varijanta FOKI sekvence VDR gena (rs2228570) kako bi se videla njena povezanost sa fenotipom preeklampsije. Studija je obuhvatila pacijente sa PE i kontrolne grupe odgovarajuće starosti regrutovane iz ginekološkog odeljenja Kombinovane vojne bolnice (CMH) u Muzafarabadu, Azad Kašmir, sprovedena je od avgusta 2021. do januara 2022. godine na Univerzitetu Kuaid-i-Azam u Islamabadu, Pakistan. Unapred dizajniran upitnik je korišćen za prikupljanje sociodemografskih informacija, kliničkih parametara, reproduktivnog zdravlja, porodične istorije hipertenzije i različitih faktora načina života kod pacijenata sa PE i kontrolne grupe. Za analizu podataka korišćen je SPSS 20. Metoda polimerazne lančane reakcije - polimorfizma dužine restrikcionih fragmenata (RFLP-PCR) je izvršena na ekstrahovanim uzorcima DNK pacijenata sa PE kako bi se ispitali genotipovi za VDR FOKI polimorfizam. Od 1933 trudnice koje su se porodile u CMH, Muzafarabad, od aprila do jula 2021. godine, kod 3,10% je dijagnostikovana

PE. Za ovu studiju slučaja i kontrole regrutovano je ukupno 300 trudnica, od kojih je 60 bilo pacijentkinja sa PE, a 240 kontrolne grupe po godinama. SPSS analiza podataka pokazala je da su porodična istorija hipertenzije i prethodna istorija pobačaja snažno povezani sa visokim rizikom od PE ($p<0,05$), dok su višestruke trudnoće i pravilan unos suplemenata tokom trudnoće snažno povezani sa smanjenim rizikom od PE kod žena Ajkuoki King ($p<0,05$). Kliničke karakteristike, tj. sistolni krvni pritisak (SKP), dijastolni krvni pritisak (DKP), alkalna fosfataza (ALP), alanin transaminaza (ALT) i proteini u urinu, bili su značajno povišeni, dok je hemoglobin u krvi bio značajno niži kod pacijenata sa PE ($p<0,0001$). Učestalost manjeg alela FOKI polimorfizma bila je veća kod pacijenata sa PE, ali nije otkrivena značajna povezanost. PE je imala učestalost od 3,10% među trudnicama koje su se pojavile u CMH u Muzafarabadu. Identifikacija pozitivne povezanosti porodične istorije hipertenzije, prethodne istorije pobačaja sa pojavom PE i visoka učestalost

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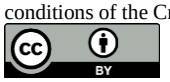

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