⇥ Research Article

Risk Factors Associated With the Occurrence of Preeclampsia in Southern Iran

Akhtar Sayadi[1] (ORCID), Zahra Hosseini[2], Ali Mouseli[3*] (ORCID), Saeide Shahsavari[4], Somayeh Hoseinvandtabar[1]

[1]Student Research Committee, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[2]Tobacco and Health Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[3]Social Determinants in Health Promotion Research Center, Research Institute for Health, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[4]Fertility and Infertility Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

Abstract

Background: Hypertension during pregnancy, along with proteinuria and organ dysfunction, causes preeclampsia, which can lead to several complications, even death in some cases for both the mother and her fetus. This study aimed to compare the risk factors of preeclampsia incidence in multipara women in Bandar Abbas.

Methods: This case-control study reviewed 215 medical records of pregnant women referring to the Persian Gulf Hospital of Bandar Abbas, Iran from April 2019 to March 2020. They reviewed the records after their classification into the case (with preeclampsia) and control (without preeclampsia) groups. Both groups were matched, and after gathering the main variables and demographic factors, the data were analyzed by SPSS, version 22.

Results: The mean age of the participants was 31.43 ± 5.04 years. There was a significant relationship between preeclampsia and chronic blood pressure (BP) ($P=0.0001$) with an odds ratio of 14.77. However, no significant association was found between liver disease ($P=1.00$), heart disease ($P=0.095$), diabetes ($P=0.053$), and kidney disease ($P=0.76$) with preeclampsia. In addition, the comparison results revealed a significant relationship between demographic variables and preeclampsia, systolic blood pressure (SBP) ($P=0.001$), and diastolic blood pressure (DBP) ($P=0.001$) with the incidence of preeclampsia.

Conclusion: The results showed that even though there was no significant relationship between diabetes, heart disease, and kidney disease with preeclampsia, patients with these diseases were 2.27, 1.21, and 6.3 times more likely to develop preeclampsia, respectively.

Keywords: Preeclampsia, Risk factors, Chronic disease, Pregnant women

*Correspondence to
Ali Mouseli,
Email: mouseli136025@
gmail.com

Background

Preeclampsia is a condition during pregnancy in which high blood pressure (BP) is associated with at least one cause of proteinuria, organ dysfunction, or manifestations of fetal growth restriction (1). According to some studies, the risk of preeclampsia in healthy women ranged from 3% to 5%, which is 1.5-2 times higher in the first pregnancy (2,3). Preeclampsia is directly responsible for 1015% of maternal death worldwide, the third leading cause of maternal mortality (2,4). Cesarean delivery, abortion, and stillbirth are among the major causes of death in women with preeclampsia (5).

The global prevalence of preeclampsia is 35% on average (6). A review study reported that the prevalence of preeclampsia in Iran was 7% by the end of 2013, while it was 4% by the end of 2005 (7). A study in Bandar Abbas reported the prevalence of preeclampsia as 5.8% (8). Different studies showed the association of several underlying diseases such as systematic lupus erythematosus (SLE) (9), kidney failure (10), diabetes

(11), and cardiovascular and liver diseases, as well as chronic BP, with preeclampsia (5,12,13). In addition, an association was found between demographic factors such as maternal blood type and Rhesus (Rh) and preeclampsia in some studies (14,15).

SLE is a multisystem autoimmune inflammatory disorder, which is more prevalent in pregnant women of late adolescence or above 40 (9,16). SLE increases the risk of preeclampsia by about four times (3,9,16). Autoimmune diseases such as SLE can cause multiorgan dysfunction, including kidney failure (17). SLE has different clinical manifestations, and skin and joint involvement are the most frequent ones. Pregnant women with SLE are at higher risk for preterm birth, preeclampsia, fetal growth restriction, fetal death, and neonatal lupus (9).

Chronic kidney disease (CKD) is one of the 20 leading causes of death worldwide (17). The prevalence of CKD in women of reproductive age in low-income countries is almost twice higher than that in high-income countries (10). Although acute renal injury (AKI) is considered a

risk factor for CKD that can lead to preeclampsia, there is still no clear explanation for the association of AKI with CKD (10,17). Low birth weight, preterm delivery, and a history of more than one pregnancy with preeclampsia exacerbate kidney problems (18). BP disorders are the most common cause of pregnancy-related AKI (10).

Chronic BP is referred to as a condition when a pregnant woman has hypertension generally or before the 20th week of gestation (5). The risk of end-stage renal disease increases four times in women with preeclampsia and chronic BP by the 10th year after pregnancy. High body mass index, a history of preeclampsia, and high BP are the major risk factors for preeclampsia (5). The comorbidity of gestational hypertension with proteinuria and organ dysfunction is not common, but it can be a risk factor for the exacerbation of preeclampsia (12). According to the American College of Obstetrics and Gynecology, even in the absence of proteinuria, the comorbidity of high BP with symptoms (e.g., neuro-visual disorders, kidney problems, thrombocytopenia, pulmonary edema, and hepatic impairment) can be considered the diagnostic criteria for preeclampsia (13).

Diabetes is also considered a risk factor for preeclampsia (5). In women with types 1 and 2 diabetes, factors such as maternal age, a history of preeclampsia, proteinuria, and hypertension are the known risk factors (13). Women with type 1 diabetes and their fetuses are at a higher risk for preeclampsia and preterm delivery (11). Women with types 1 (15-20%), 2 (10-14%), and gestational (2-10%) diabetes are more prone to develop preeclampsia than non-diabetic ones.[13]

If preeclampsia exacerbates and develops eclampsia, it is life-threatening for both the mother and her fetus. The termination of pregnancy is currently the only way to manage preeclampsia, while it is associated with metabolic, cardiovascular, and renal complications for both the mother and her fetus in the future (12).

Objectives

The consequences of preeclampsia should be effectively prevented by the timely detection and identification of potential diseases and health problems in women of reproductive age. To the best of our knowledge, no study has so far focused on the role of underlying diseases in the incidence of preeclampsia in women in Bandar Abbas, Iran. Accordingly, the present study aimed at comparing risk factors in the incidence of preeclampsia among multipara women in Bandar Abbas in 2019.

Methods
Study Design
In the present case-control study, chronic diseases and factors associated with preeclampsia were evaluated in pregnant women referring to the Persian Gulf Hospital of

Bandar Abbas, Iran from April 2019 to March 2020. This paper is the result of a research project confirmed by the Student Research Committee of Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

Study Participants
The sample size for each case (women with preeclampsia) and control (women without preeclampsia) group was determined 100 based on the results of the study by Hashemi et al using the formula of $n=2(Z_{1-\frac{\alpha}{2}} + Z_{1} - \beta)^2 SD^2$ and considering $\alpha = 0.05$ and $d = 0.03$ (19). After obtaining the required permissions from Hormozgan University of Medical Sciences and the Persian Gulf Hospital of Bandar Abbas, to collect data from the medical records of the study participants, the researcher referred to the Archives Department of the hospital. Therefore, both case and control groups were matched with the following items at the time of the study:

Second pregnancy onwards, single pregnancy, no history of preeclampsia, no history of polycystic ovary, no history of organ transplantation, no history of preeclampsia in the 1st-degree relatives, no sickle cell disease, the age range of 20-40 years (20,21). Preeclampsia was the only difference between the case and control groups.

Data Collection Instruments
The data of the medical records of the hospital clients were entered into a researcher-made checklist supervised and approved by professors in order to find an association between demographic variables (e.g., maternal age and BP at the time of the diagnosis of preeclampsia, number of pregnancies and deliveries, history and number of abortions, type of previous delivery, maternal blood type, and Rh) and preeclampsia. Further, the main variables entered into the checklist included cardiovascular, liver, and kidney disorders, diabetes, SLE, and chronic BP (20); these complications were considered as the inclusion criterion, and eligible subjects had to have at least one of them. After the collection of data from the medical records of pregnant women, due to incomplete documentation and the need for the substitution of other variables for missing data, finally, 215 medical records were included in the study, of which 117 were the controls, and the remaining 98 ones were related to cases.

Data Analysis
Descriptive statistics were used to express quantitative data. The chi-square test was employed to evaluate a relationship between the main and demographic variables and preeclampsia. Multiple logistic regression with a 95% confidence interval was applied to find the potential of developing preeclampsia by the main and demographic variables. All data were analyzed using SPSS (version 22) by a statistical expert, and $P < 0.05$ was considered

statistically significant.

Results

The mean age of the study participants was 31.43±5.014 years. There were 98 available preeclampsia cases, all of which were studied to get closer to the quorum set for the case group (100 cases); therefore, a few cases over the age of 40 were studied as well. The mean systolic blood pressure (SBP) of the participants was 124.94 ± 19.54 mm Hg, ranging from 90 to 190. The maternal diastolic blood pressure (DBP) also ranged from 60 to 120 mm Hg, with a mean of 80.06 ± 13.18. The mean of SBP and DBP in the case group were 137.05 and 87.73 mm Hg, respectively (Table 1), which is slightly lower than the BP required to diagnose preeclampsia. The researchers had no involvement in diagnosing preeclampsia cases and only extracted and studied the information in the files. The mean number of pregnancies was 3.30 ±1.38, ranging from 2 to 8. The mean number of deliveries was 1.84 ± 1.18, ranging from 0 to 7. Table 1 presents the distribution of demographic variables.

The results of logistic regression showed that chronic BP ($P = 0.0001$) had a significant difference between the two groups, and according to its odds ratio (OR) value, the risk of preeclampsia was higher in pregnant women with a history of chronic BP (OR = 14.77). There was also an insignificant relationship between liver disease ($P = 1.00$), heart disease ($P = 0.095$), diabetes ($P = 0.053$), kidney disease ($P = 0.76$), and preeclampsia ($P < 0.05$). However, based on the logistic regression test, the chances of developing preeclampsia in people with diabetes, heart disease, and kidney disease were 2.27, 1.21, and 6.30, respectively. None of the subjects had SLE, and no significant difference was found between the two groups in this regard (Table 2).

According to Table 1, the frequency of normal vaginal delivery (NVD) and cesarean deliveries in the case and control groups were 65.3% and 74.4%, as well as 33.7% and 25.6%, respectively; however, data in Table 3 demonstrate no significant differences between the two groups ($P = 0.182$). The mean number of deliveries in the case and control groups was 1.91 and 1.87, respectively, and no significant difference was found between the two groups ($P = 0.43$). The result represented no significant correlation between the history of abortion and preeclampsia ($P = 0.26$). The distribution of blood types was almost the same in both groups so that the frequency of blood types A, B, AB, and O in the case and control groups was 23.5%, 23.9%, 25.5%, and 29.1%, as well as 10.2%, 8.5%, 39.8%, and 36.8%, respectively. There was no significant relationship between blood type and preeclampsia (Table 3). The frequency of Rh+ and Rh- was 92.9% and 95.7%, as well as 6.1% and 3.4%, in the case and control groups, respectively, indicating a distribution pattern similar to that of blood types, and no significant

difference was observed between the groups ($P = 0.35$). Among the demographic variables, SBP and DBP ($P = 0.001$) indicated a significant relationship with the

Table 1. Descriptive Table of Demographic Variables

Variable	Case Group	Control Group	Mean
Age	23.10	30.87	31.43 ± 5.014
Systolic blood pressure	137.05	114.81	124.94 ± 19.54
Diastolic blood pressure	87.73	73.65	80.06 ± 13.18
Frequency of pregnancy	3.46	3.16	3.30 ± 1.38
Number of delivery	1.91	1.78	1.84 ± 1.18
History of abortion			
Yes	42 (42.9%)	41 (35%)	-
No	56 (57.1%)	75 (64.1%)	
Frequency of abortion	0.55	1.39	0.81 ± 0.867
Type of previous delivery			
Cesarean section	33 (33.7%)	30 (25.6%)	-
NVD	64 (65.3%)	87 (74.4%)	
Blood group			
A	23 (23.5%)	28 (23.9%)	
B	25 (25.5%)	34 (29.1%)	
AB	10 (10.2%)	10 (8.5%)	-
O	39 (39.8%)	43 (36.8%)	
Rh			
Positive	91 (92.9%)	112 (95.7%)	-
Negative	6 (6.1%)	4 (3.4%)	

Note. NVD: Normal vaginal delivery; Rh: Rhesus.

Table 2. Logistic Regression Analysis for Main Variables in the Study

Variable	No. (%)	P Value	OR	95% CI
Heart disease				
Yes	6 (2.8)	0.095	6.30	0.72-54.90
No	208 (96.7)		Reference	
CKD				
Yes	10 (4.7)	0.76	1.21	0.34-4.33
No	204 (94.9)		Reference	
Chronic blood pressure				
Yes	54 (25.1)	0.0001*	14.77	6.24-34.96
No	160 (74.7)		Reference	
Liver disorders				
Yes	3(1.4)	1.00	-	-
No	210 (97.7)			
Diabetes				
Yes	27 (12.6)	0.053	2.27	0.98-5.23
No	187 (87)		Reference	
SLE				
Yes	0 (0)	-	-	-
No	215 (100)			

Note. OR: Odds ratio; CI: Confidence interval; CKD: Chronic kidney disease; SLE: Systemic lupus erythematosus.

Table 3. Logistic Regression Analysis for Main Variables of the Study

Variable	P Value	OR	95% CI
Age	0.074	1.05	0.99-1.11
Systolic blood pressure	0.001	1.09	1.06-1.11
Diastolic blood pressure	0.001	1.11	1.08-1.15
Frequency of pregnancy	0.119	1.17	0.96-1.42
Number of delivery	0.43	1.97	0.86-1.38
History of abortion			
Yes	0.26	1.37	0.79-2.38
No		Reference	
Type of previous delivery			
Cesarean section	0.182	0.66	0.37-1.20
NVD		Reference	
Blood group			
A	0.78	0.90	0.94-1.82
B	0.54	0.811	0.41-1.59
AB	0.84	1.10	0.41-2.93
O		Reference	
Rh			
Positive	0.35	0.54	0.14-1.9
Negative		Reference	

Note. NVD: Normal vaginal delivery; OR: Odd ratio; CI: Confidence interval.

incidence of preeclampsia, and the OR of preeclampsia was the same in both groups (Table 3).

Discussion

Preeclampsia is a heterogeneous disease with not entirely understood etiology. Numerous factors are suggested to confirm preeclampsia, including chronic hypertension, kidney disease, diabetes, and the like (22). The results of the present study on the medical records of pregnant women in Bandar Abbas in 2019 confirmed a significant relationship between some chronic diseases and preeclampsia.

Chronic Blood Pressure

A significant difference was observed in chronic BP between the case and control groups in the present study, which is consistent with the finding of Hashemi et al (19) on the relationship between chronic BP and preeclampsia and that of Boriboonhirunsarn et al at the Royal Thai College of Obstetricians and Gynecologists (5). Miller et al also reported that chronic BP could increase the risk of pregnancy-associated stroke by three times (23). In pre-eclampsia, the interaction between the maternal constitution and the placenta is influenced by environmental factors and genetics, causing a hypertensive inflammatory response (24). Based on the comparison of sub-variables in the present study, a significant difference was found between the two groups in terms of SBP and DBP, which is in line with the findings of Hashemi et al (19).

Liver Disease

Although all subjects with liver disease were in the case group in the present study, no significant difference was found between the two groups in terms of the association of this variable with preeclampsia. The results of the studies by Frank Wolf et al (2) and Ammon et al (25) are inconsistent with those of the present study. Alese et al recommended that some non-invasive tests such as total cholesterol, non-high-density lipoprotein cholesterol, triglyceride, and liver enzymes aspartate transaminase and alanine transaminase should be routinely performed for pregnant mothers to predict the onset of preeclampsia in the first trimester (26).

Heart Disease

In the current study, the association between heart disease and preeclampsia was not significant, but the results represented that heart disease could increase the risk of preeclampsia by six times (OR=6.30, CI=0.72-54.90). The results of Cunningham et al demonstrated that preeclampsia increases the risk of stroke and ischemic heart disease (12). A 10-year prospective study by Hashemi et al indicated the increased risk of heart disease in women with a history of preeclampsia (19).

Diabetes

In the present study, there was no significant difference between the two groups in terms of the relationship between diabetes and the incidence of preeclampsia. However, the risk of preeclampsia in women with diabetes was twice higher than that of those without diabetics (OR=2.27, CI=0.98-5.23), which corroborates the findings of the prospective study by Hashemi et al, reporting that the risk of preeclampsia was three times higher in women with type 2 diabetes than those without diabetes (19). Conversely, Košir Pogačnik et al found no significant association between gestational diabetes and preeclampsia (27), which conforms to the results of the current study. In another study, Vestgaard et al concluded that the prevalence of preeclampsia in women with type 1 diabetes was 5-6 times higher than in the general population (28).

Chronic Kidney Disease

CKD was another main variable of the present study in terms of its association with preeclampsia, and the association between these variables showed no significant difference between the two groups (OR=1.21, CI=0.34-4.33). The results of Conti-Ramsden et al (10) and Khashan et al (1) contradict those of the current study in terms of the association of renal failure with preeclampsia.

Systematic Lupus Erythematosus

Based on the results of Dong et al, the prevalence of preeclampsia in patients with a history of lupus

erythematosus was twice higher than that of healthy individuals (3). Simard et al and Do & Druzin also reported lupus erythematosus as a risk factor for preeclampsia (9,16); however, none of the present study subjects had lupus.

Type of Delivery
Comparing the previous type of delivery, the results revealed that the majority of subjects in both groups had NVD. The results of statistical analyses also demonstrated no significant difference with regard to this variable between the two groups, and the type of previous delivery had a slight impact on the risk of developing preeclampsia (OR = 0.66, CI = 0.37-1.20). Sukmawati et al reported that the frequency of cesarean delivery is higher in women with preeclampsia (29), which is consistent with the result of Cho et al (30), but contradicts the finding of the present study. One of the inclusion criteria of the current study was the lack of a history of preeclampsia; this might be considered a reason for the higher prevalence of natural deliveries compared to the cesarean section in previous pregnancies because the termination of pregnancy is the only available therapeutic strategy for preeclampsia performed through cesarean section (12).

Blood Type and Rh
The results of the present study showed no significant difference between the two groups in terms of the association of blood type and Rh with preeclampsia, which is in line with the results of Aghasadeghi and Saadat (14). The findings of a study by Jin et al on more than 1.5 million pregnant women in Korea represented that there was no significant association between Rh and preeclampsia (31). However, in the study by Avci et al, blood type AB indicated a significant association with preeclampsia. They also reported a significant relationship between Rh+ and increased BP in the participants (15).

Due to the importance of the health of pregnant mothers, the results of this study are highly useful for health workers because it has reviewed the case of all mothers with preeclampsia for a year and has addressed the underlying factors in an integrated and comprehensive manner. This idea is innovative in research. A key strength of the present study was that it was the first study in Bandar Abbas which matched case and control groups using powerful match factors defined in the Methods Section to identify the impact of the mentioned disease. Although health care centers are good units to access information about pregnant women, we were limited and deprived because of the large workload of those centers working on COVID-19 at the time of this study and only examined the Persian Gulf Hospital of Bandar Abbas. Further, due to the lack of the registration of some indicators such as body mass index completely in all patients' files, there was a limit for its review in this study. Thus, it is suggested that

future prospective studies be conducted to investigate the most important factors associated with the incidence of preeclampsia in different populations. Another limitation of this study was that none of the pregnant mothers had SLE. Therefore, it was impossible to compare the findings of this study with those of other studies in terms of incidence and its relationship with the incidence of preeclampsia.

Conclusion
Considering the pivotal role of preeclampsia in maternal and fetus complications and disorders, and due to the increased susceptibility to preeclampsia in people with diabetes, heart, and kidney diseases, it is recommended that the necessary measures be taken for the timely diagnosis and prevention of complications. Given that no prophylaxis/treatment has yet been reported for preeclampsia other than the termination of pregnancy, experts are advised to focus more on predicting the occurrence of preeclampsia in pregnant women. Future studies should focus on performing intervention programs in pregnant women to reduce the risk of preeclampsia.

Authors' Contribution
Conceptualization: Akhtar Sayadi, Zahra Hosseini.
Data Curation: Akhtar Sayadi.
Formal Analysis: Akhtar Sayadi, Zahra Hosseini, Ali Mouseli.
Funding Acquisition: Akhtar Sayadi.
Investigation: Akhtar Sayadi. Ali Mouseli.
Methodology: Akhtar Sayadi, Zahra Hosseini.
Project Administration: Akhtar Sayadi.
Resources: Akhtar Sayadi, Saeide Shahsavari.
Software: Somayeh Hoseinvandtabar.
Supervision: Ali Mouseli, Zahra Hosseini.
Validation: Ali Mouseli, Zahra Hosseini.
Visualization: Akhtar Sayadi, Zahra Hosseini, Ali Mouseli.
Writing – Original Draft: Akhtar Sayadi , Saeide Shahsavari, Somayeh Hoseinvandtabar.
Writing – Review & Editing: Akhtar Sayadi, Zahra Hosseini, Ali Mouseli.

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