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Risk Factors for Pre-Eclampsia

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Abstract

Purpose: To identify the risk factors for pre-eclampsia (PE).

Material and methods: This case-control study was carried out between 3rd January and 30th April 2020 in three University Teaching Hospitals. Nursing mothers who had PE or not were recruited and some data analyzed. The main variables analyzed included maternal age and parity, marital status, maternal past-history of PE or hypertension, contraception used before conception, eventuality of pregnancy from a new sexual partner (NSP), health care provider, number of fetuses delivered and umbilical cord insertion. Fisher's exact test, t-test and logistic regression were used for comparison. P<0.05 was considered statistically significant.

Results: Of 2019 pregnant women, 141 had PE (7.0%). Significant risk factors for PE were maternal past-history of hypertension (aOR 17.76, 95%CI 4.34-37.50, P<0.001), pregnancy from a NSP (aOR 9.55, 95%CI 1.94-46.87, P=0.005), nulliparity (aOR 3.04, 95%CI 1.76-5.27, P<0.001), marginal umbilical cord insertion (MCI) (aOR 2.87, 95%CI 1.34-6.16, P=0.007) and pregnancy following >12 months of contraception with condom (aOR 2.61, 95%CI 1.35-5.08, P= 0.004).

Conclusion: This survey revealed that chronic hypertension, pregnancy from a NSP, nulliparity, MCI and pregnancy following >12 months of contraception with condom were risk factors for PE. Therefore, close attention should be paid during pregnancy, labor and in the puerperium to women with the above-mentioned risk factors.

Keywords: Nulliparity; Past-history of hypertension; Pre-eclampsia; Risk factors; Pregnancy from a new sexual partner

List of abbreviations: ANC: Antenatal care, aOR: adjusted odds ratio; CI: Confidence interval; HDP: Hypertensive disorders in pregnancy; IUFD: Intra-uterine fetal death; IUGR: Intra-uterine growth restriction; LBW: Low birth weight; MCI: Marginal umbilical cord insertion; NICU: Neonatal intensive care unit; NSP: New sexual partner; OR: Odds ratio; PE: Pre-eclampsia

Introduction

T Hypertensive disorders in pregnancy (HDP) represent one of the major causes of maternal mortality and severe maternal morbidity. It comprises chronic hypertension, gestational hypertension, pre-eclampsia (PE) - eclampsia and superimposed PE-eclampsia. The rate of HDP ranges between 5% and 10% [1,2]. Rate as high as 16.8% has been observed in Ethiopia [3]. Amongst HDP, PE is the most associated with adverse maternal and perinatal outcome [4].

PE is defined as hypertension occurring at ≥20 weeks gestation with one or more of the following: significant proteinuria, acute kidney injury, liver dysfunction, neurological features, hemolysis, thrombocytopenia, fetal growth restriction [4]. Its incidence ranges between 5% and 10% worldwide [5-7].

The pathogenesis of PE is linked to the failure of invasion of the intra-myometrial muscular layer segments of the spiral arteries between the 12th and the 16th weeks of gestation. The result is placental ischemia with production of vasoactive substances such as endothelin-1 [8]. The causes of the poor invasion of spiral arteries are not well known.

Complications of PE are numerous. Maternal complications include cerebro-vascular accident, retinal detachment, acute kidney injury and even maternal death. Fetal complications are intra-uterine growth restriction (IUGR), placenta abruption, intra-uterine fetal death (IUFD), birth asphyxia, low birth weight (LBW), transfer of the newborn to the neonatal intensive care unit (NICU) and neonatal death [9,10].

Prevention of PE can be done with 1.5 g of calcium or with 120-150mg of acetylsalicylic acid daily. Acetylsalicylic acid administration as from the 20th week of gestation is associated with a 50% reduction in the risk of PE [11]. For prevention to be more efficient, women at risk should be targeted. Although the etiologies are unknown, some risk factors for PE are well known. They include nulliparity, advanced maternal age, multiple pregnancy, systemic lupus erythematosus, (pre-gestational) diabetes mellitus, family history of hypertension and fertility treatments [12,13].

The risk factors might vary from one setting to another. Knowing the risk factors in our environment might help us in better preventing or diagnosing some cases earlier. To the best of our knowledge, no study has been carried out in our environment. That is why we decided to carry out this one which aimed at seeking for these risk factors.

Methods

This case-control study was carried out between 3rd January and 30th April 2020 in three University Teaching Hospitals. Nursing mothers who had PE from the 28th complete week of pregnancy to 48 hours after delivery (group A) were recruited. The diagnosis of PE was based on the presence of blood pressure of ≥140/90 mm Hg that occurred at ≥20th week of gestation associated with a significant proteinuria (≥300 mg/24h), with or without acute kidney injury, liver dysfunction, neurological features, hemolysis, thrombocytopenia or fetal growth restriction.

For each nursing mother who had PE, three other nursing mothers who developed no PE throughout pregnancy till 48 hours after delivery (group B) and who delivered just after the woman with PE were also recruited. We decided to recruit three controls for each case to increase the power of our study. Women with incomplete files were excluded. This study received approval from the Ethics committee of the Faculty of Medicine. All women gave their informed written consent.

The variables recorded among all women included maternal age at delivery, parity, gestational age at delivery (confirmed by an ultrasound scan performed before 20 weeks gestation), past-history of hypertension (blood pressure ≥140/90 mmHg diagnosed outside pregnancy or before the 20th week of gestation [14]) or diabetes mellitus (fasting blood sugar ≥126 mg/dL [15]), contraception being used before conception, if any, if it was a new sexual partner (NSP) (partner responsible for the current pregnancy

was a new one), heath care provider who performed antenatal visits (whether it was a nurse, a midwife, a general practitioner or an obstetrician), alcohol consumption, residence (rural or urban), the number of fetuses delivered, presence or not of marginal cord insertion (MCI) at placenta examination (MCI was defined as the insertion of the umbilical cord with its external margin at less than 2 cm from that of the placenta [16]), birth and placenta weights and sex of newborn. Some other variables were recorded in women who had PE. This included gestational age at diagnosis, magnesium sulfate administration and severity of the disease (severe PE was defined as blood pressure ≥160/110 mmHg with one or more of the following: headache, visual disturbances, epigastric pain or oliguria [17]).

Our minimum sample size of 45 women with PE was calculated using the following formula $N = 2\times(Z\alpha+Z\beta/P_0-P_1)^2\times P\times(1-P)$ [18], where $Z\alpha = 1.65$ corresponds to a type I error of 5%, $Z\beta = 1.96$ corresponds to a power or 97.5%, P0 the proportion of 25-hydroxy vitamin D deficiency in patients with PE (27.6%) [19], P1 the proportion of 25-hydroxy vitamin D deficiency in patients without PE (0.9%) [19] and P is $(P_0+P_1)/2$.

Data were analyzed using SPSS 23.0. Data of women of group A were compared to those of women of group B. Fisher exact test was used to compare categorical variables and t-test to compare continuous variables. We used odds ratios with their 95% confidence intervals (CIs) to present the comparison between the two groups. Logistic regression was used to control for confounders. $P<0.05$ was considered statistically significant.

Results

During the period under study, 141 nursing mothers out of 2,019 have had PE, giving an incidence of 7.0%. But, 44 files of women with PE were excluded for incompleteness. The 97 files remaining (group A) and those of 291 women without PE (group B) were analyzed.

Some sociodemographic and obstetrical variables are shown in Table 1.

Variables	Women (n=97) of group A N (%)	Women (n=291) of group B N (%)	OR	95% CI	P-value
Mother's age* (y)	28.9 ± 6.6 (16-42)	28.8 ± 5.9 (17-43)	-	-	0.888
Parity*	1.1 ± 1.6 (0-7)	1.4 ± 1.5 (0-9)	-	-	0.094
Maternal age ≥35	20 (20.6)	46 (15.8)	1.38	0.77-2.48	0.174
Patient's past-history of chronic hypertension	12 (12.4)	7 (3.8)	3.59	1.53-8.43	0.003
pregnancy following >12 months condom use	25 (25.8)	35 (12.0)	2.54	1.42-4.51	0.001
Pregnancy from a NSP	10 (10.3)	2 (0.7)	16.60	3.57-77.24	<0.001
Multiple pregnancy	6 (6.2)	8 (2.7)	2.33	0.79-6.32	0.107
Calcium supplementation	42 (43.3)	129 (44.3)	0.95	0.60-1.52	0.477
Acetylsalicylic acid supplementation	2 (2.0)	5 (1.7)	1.2	0.23-6.30	0.556
Pregnancy followed up by a nurse	9 (9.3)	14 (4.8)	2.02	0.84-4.83	0.089
Marginal cord insertion	17 (17.5)	25 (8.6)	2.26	1.16-4.39	0.014

*Mean ± SD (range),

OR: Odds ratio, CI: Confidence interval, SD: Standard deviation, NSP: New sexual partner

Table 1: Some sociodemographic characteristics of the population under study

Mean gestational age at diagnosis of PE was 34.4 ± 3.7 (range: 28-43) with diagnosis of PE between 34 and 43 weeks in 65 women (67.0%). PE was diagnosed in the early postpartum period (within 24 hours after delivery) in four women (4.1%). The majority of women had severe PE at diagnosis (58/97 or 59.8%). Also, in 17 cases, preeclampsia evolved to eclampsia (17.5%).

Single women were found more among women with PE (52 or 53.6% vs 144 or 49.5%, OR 1.17, 95%CI 0.74-1.86), but the difference was statistically insignificant (P=0.279). There was also no association between PE and adolescence (maternal age <20) (10 or 10.3% vs 18 or 6.2%, OR 1.74, 95%CI 0.77-3.91, P=0.139), urban residence (95 or 97.9% vs 274 or 94.2%, OR 2.94, 95%CI 0.66-12.99, P=0.105) or alcohol consumption (10 or 10.3% vs 18 or 6.2%, OR 1.74, 95%CI 0.77-3.91, P=0.130).

ANCs in women of group A were mainly carried out by obstetricians (42/97 or 43.3%) and nurses (34 or 35.1%). PE prevention using 1.5 g of calcium daily was mainly done by obstetricians than nurses (24/42 or 57.1% vs 9/34 or 26.5%, P=0.006). No difference was observed between the two groups as concerns prevention using 120 to 150 mg of acetylsalicylic acid daily (4.8% vs 0%, P=0.302). Prevention of eclampsia using magnesium sulfate was done only in cases of severe PE (n=58).

Women with PE had lesser ANC visits (4.4 ± 1.8 vs 5.6 ± 2.2, P<0.001), advanced gestational age at booking (18.1 ± 6.6 weeks vs 16.3 ± 6.7 weeks, P=0.022). Amongst women with PE, 29 (29.1%) had less than four visits, and only three women (3.1%) had at least eight visits. Women with less than eight visits were therefore found more in women with PE (94 or 96.9% vs 232 or 79.7%, P<0.001). PE in a previous pregnancy was not a risk factor for recurrence (7 or 7.2% vs 11 or 3.8%, OR 1.98, 95%CI 0.77-4.78, P=0.133).

Family past-history of hypertension was a risk factor for PE (29 or 29.9% vs 44 or 15.1%, OR 2.39, 95%CI 1.39-4.10, P=0.001). Nulliparous women were more at risk of PE (Table 2).

Parity	Women (n=97) of group A N (%)	Women (n=291) of group B N (%)	OR	95% CI	P-value
0	55 (56.7)	100 (34.4)	2.50	1.56-3.99	<0.001
1	10 (10.3)	74 (25.4)	0.33	0.16-0.68	<0.001
2-3	24 (24.7)	88 (30.2)	0.76	0.44-1.28	0.183
4-5	6 (6.2)	25 (8.6)	0.70	0.27-1.76	0.302
≥6	2 (2.1)	4 (1.4)	1.51	0.27-8.38	0.467

OR: Odds ratio, CI: Confidence interval

Table 2: Distribution of parities of amongst the study population

Adverse outcome	OR	95%CI	P-value	aOR	95%CI	P-value
Maternal past-history of hypertension	3.59	1.53-8.43	0.003	17.76	4.34-37.50	<0.001
Pregnancy from a NSP	16.60	3.57-77.24	<0.001	9.55	1.94-46.87	0.005
Nulliparity	2.50	1.56-3.99	<0.001	3.04	1.76-5.27	<0.001
Marginal cord insertion	2.26	1.16-4.39	0.014	2.87	1.34-6.16	0.007
Pregnancy after >12 months CU	2.54	1.42-4.51	0.001	2.61	1.35-5.08	0.004
Familial past-history of hypertension	2.39	1.39-4.10	0.001	1.25	0.78-2.85	0.190

OR: Odds ratio, aOR: adjusted OR, CI: Confidence interval, CU: Condom use, NSP: New sexual partner

Table 3: Risk factors for PE after logistic regression

Amongst the 58 women with severe PE, despite magnesium sulfate administration, 12 (20.7%) had eclampsia as compared to 5/39 women (12.8%) with non-severe PE who received no magnesium sulfate.

Table 3 shows the significant risk factors for PE after logistic regression.

Discussion

Our results showed a prevalence of PE in the third trimester of pregnancy of 7.0%. Significant risk factors for PE were maternal past-history of hypertension, pregnancy from a NSP, nulliparity, MCI and pregnancy following >12 months of contraception with condom.

Our prevalence of PE is similar to the 7% rate noticed in Nigeria [20]. We observed no association between maternal age, residence, marital status, health care provider and PE. Some authors found advanced maternal age as a risk factor for PE in Israel [12].

Women with multiple pregnancies were at increased risk of PE in our series (RR 2.33, 95%CI 0.79-6.32), though statistically insignificant (P=0.107). Some researchers found that twin pregnancy was a risk factor for PE [12]. The absence of significance in our series might be due to our small sample size given that we had only 14 cases of twin pregnancies. Soluble fms-like tyrosine kinase 1 (sFlt1), which is a circulating antiangiogenic molecule produced by placental plays a main role in preeclampsia by antagonizing placental growth factor and vascular endothelial growth factor. The high circulating levels of sFlt1 due to increased placental weight explains the raised risk of PE in twin pregnancy [21]. Women with multiple gestations should be regularly screened for PE.

We also found no association between PE and past-history of PE, contrarily to what observed by Musa in Nigeria [6]. Nevertheless, women with chronic hypertension were at risk of PE, as observed in Israel by some researchers [12]. Therefore, screening for PE should be regularly done amongst women with chronic hypertension.

Nulliparity was also found in our series to be a risk factor for PE, as observed in Israel [22]. It might be explained by the underdeveloped maternal tolerance to paternally-derived trophoblast antigens [23]. Nulliparous women should be encouraged to attain frequently antenatal visits to permit early diagnosis and management of PE.

Pregnancy from a NSP was also a risk factor in our series. This has already been documented in Mexico [24]. The explanation is the same as for nulliparity [23]. Women with a NSP should attain frequently antenatal visits to permit early diagnosis of PE. Moreover, physicians should frequently screen for PE women with a NSP.

MCI was another risk factor, as observed in our units in a previous study [25] and in Norway [26]. It can be explained by the poor placenta development and perfusion in MCI which leads to placenta ischemia with increased production of vasoactive substances such as endothelin-1 [8]. MCI can be diagnosed ultrasonographically as from the 18th week of gestation [27]. Pregnancies complicated with MCI should be well followed up and screening of PE should be frequently performed.

Finally, pregnancy following >12 months of contraception with condom was another risk factor, as observed in Mexico [20], PE here is also attributed to underdeveloped maternal tolerance to paternally-derived trophoblast antigens [23]. Women should be advised to start using a contraceptive method other than condoms at least 12 months before conception. Non-barrier methods or the exposure of women to the paternal spermatic antigens is protective against PE [24]. However, no association was found between PE and pre-pregnancy condom use in Pakistan [13].

We found no association between severity of PE and occurrence of eclampsia. It might be attributed in our series to the administration of magnesium sulfate to women with severe PE. Nevertheless, we observed in our series that women with non-severe PE could also evolve to eclampsia.

Our limitations are the small sample size due to the incomplete files excluded. Moreover, we could not confirm the veracity of some answers given by women, especially as concerns the use of condom. Also, some minor cases of PE might have occurred after 48 hours after delivery. Finally, we could not be certain of the absence of any association between severity of PE and eclampsia, due to the administration of magnesium sulfate to women with severe PE for prevention of eclampsia.

Conclusion

This survey revealed that chronic hypertension, pregnancy from a NSP, nulliparity, MCI and pregnancy following >12 months of contraception with condom were risk factors for PE. Therefore, emphasis should be done amongst these women as regards the prevention means. Moreover, close attention should be paid during pregnancy, labor and in the puerperium to women with the above-mentioned risk factors to earlier diagnose and manage PE appropriately, in order to reduce maternal and perinatal adverse outcomes.

Conflicts of interest

The authors have no conflicts of interest to declare.

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