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Increased Risk of Pre-Eclampsia (PE) Among Women with the History of Migraine

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ABSTRACT

The Objective of this study was to assess possible association of history of migraine with pre-eclampsia (PE). This was a retrospective study to compare history of migraine in 90 women affected by PE with 90 women without PE as the control group. They recruited by a nonrandomized consecutive sampling method. Data were collected by a questionnaire including demographic, medical, obstetrics, and migraine assessment sections. Data were analyzed using SPSS. Results showed an increased risk of PE in women with history of migraine (odds ratio: 2.87; $p < 0.05$). Result demonstrated that migraine history in the case group is 14/4% and in control group is 5/6%. Gestational age (GA) at delivery and weight of neonate (WN) were significantly lower compared to control (GA: 37.3 ± 2.6 vs. 38.7 ± 1.3 weeks T test; $P < 0.01$) (WN: 2930 ± 690 vs. 3330 ± 420; T test; $P < 0.0$). Cesarean section was more frequent in the PE group compared to the control group [37 (42%) vs. 14 (15.6%)]; chi square; $p < 0.01$]. The association of migraine with PE is the result of some similar mechanism leading to endothelial dysfunction. Frequent reports of an association between migraine and PE in different populations suggest a history of migraine as a risk factor for PE/gestational hypertension (GH).

KEYWORDS: migraine; pre-eclampsia; pregnancy

INTRODUCTION

Hypertensive disorders of pregnancy with the overall incidence of 5.9% (1) remains the leading cause of direct maternal deaths in many countries (2,3). Pre-eclampsia (PE) is demonstrated to be a major cause of poor outcome in pregnancy. It is associated with fetal growth restriction, low birth weight, preterm delivery, respiratory distress syndrome, and admission to neonatal intensive care, diminished amniotic fluid, and altered oxygenation (4–6). Hypertensive disorders of pregnancy are classified as PE, eclampsia, gestational hypertension (GH), chronic hypertension, and PE superimposed on chronic hypertension (7). Pre-eclampsia occurs after midgestation, is defined by the *de novo* appearance of hypertension (systolic blood pressure (SBP) of ≥140 mm Hg or diastolic blood pressure (DBP) of ≥ 90 mm Hg), accompanied by a new of onset proteinuria, and defined as ≥ 300 mg per 24 h.

Pre-eclampsia is a multisystem disorder, unique to pregnancy (8). The mechanisms responsible for the pathogenesis of PE are poorly understood. It is supposed to be determined by two essential processes—the first given by a superficial trophoblastic invasion and a poor remodeling of the spiral arteries and the maternal deciduas (9). Alterations in endothelial cell function by activating agents produced by the placenta are proposed to initiate the clinical syndromes of PE. Circulating factors, such as inflammatory cytokines, are shown to be elevated in pre-eclamptic women and are proposed to be important links between placental ischemia and endothelial dysfunction (10).

Migraine is a chronic, often-inherited condition involving brain hypersensitivity and a lowered threshold for trigeminal-vascular activation (11) results in a marked decrease in a patient's quality of life (12). Migraine can be divided into two major subtypes: 1) migraine without aura and 2) migraine with aura (13). The prevalence of migraine was 17.1% in women and 5.6% in men Migraine is one of the most common

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neurological disorders in adult women (14) which means a female/male prevalence ratio of 3:1. This prevalence rises from 4% before puberty to a peak of 25% in women during their child-bearing years with a decrease after menopause (15,16).

The pathophysiology of migraine headaches is not clearly understood. Growing evidence supports the role of neurogenic peptides, such as serotonin and dopamine, in the brain. These vasoactive neuropeptides stimulate an inflammatory cascade with the release of endothelial cells, mast cells, and platelets. This inflammation causes vasodilation and a perivascular reaction (17).

Association of migraine with PE has been assessed from 1954. This cross-sectional study showed that 21.4% of migraneous pregnant women develop toxemia (18). However, the next case-control study showed no difference between women in migraneous and control groups reporting a history of toxemia (19). One subsequent cohort study (20) and another case control study (21) showed that women with migraine have higher chance of developing PE.

In addition, a history of migraine was associated with an increased risk of PE in pregnant women (22–26). Adeny and Williams (27) reviewed 10 studies addressing the association between migraine and PE and/or GH. Of the 10 studies, 8 reported a positive association. They recommend more rigorous studies to clarify the relationship. Although most of these studies showed a positive association between migraine and PE, the criteria to diagnosis and classification of PE and migraine was extensively different. Allias et al. (28) discussed migraine as a risk factor in pregnancy and suggest further research to assess the existence and extent of the risks posed by migraine during pregnancy.

This study aims to assess the association between migraine and PE, using conventional rigorous criteria for diagnosis and classification of PE and migraine in an Iranian population.

MATERIAL AND METHODS

This was a retrospective case control study of 180 women in two groups of 90, in the post-partum unit of Kashan University hospitals. They subjects have only a single fetus and should have no history of chronic hypertension or other medical diseases. They should have at least eight prenatal visits during pregnancy with two visits occurring before the 20th week of pregnancy. The patients should have no report of hypertension in their PNC care visits before the 20th week of pregnancy. They were recruited for the study if they met this inclusion criteria for the study, and if following an explanation about the study, they gave us written consent. The Ethical Committee of Shahid Beheshti Medical Science University and Kashan Medical Science University confirmed the study.

With a convenience sampling method, 90 women with recorded PE (cases group) were recruited in post-partum units of two Kashan University Hospitals. The criteria to diagnose and classification of PE was based on the Report of the National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy (29). Based on the NHBPEP Report, PE is a pregnancy-specific syndrome that usually occurs after 20 weeks of gestation. It presents as *de novo* hypertension (SBP of ≥ 140 mmHg and/or DBP of ≥ 90 mmHg) on two occasions, 6 h apart, accompanied by a new onset of proteinuria defined as ≥ 300 mg/24 h (29, 30).

Criteria for the diagnosis of migraine was a provided questionnaire based on the Headache International Association (13) (Figure 1). If the subjects were diagnosed as migraneous based on ICHD-II, they were referred to the neurologist for further assessment and the final confirmation of migraine. Women with migraine were also asked about the average number of migraines in a month, their age of migraine initiation, duration and intensity of headaches, and migraine occurrence in menstruation. The tool for data collection consisted of three sections of a demographic questionnaire, a checklist to assess hypertension, and a checklist to assess migraine. Content validity and test-retest was performed to assess validity and reliability of the questionnaires. Data was analyzed by SPSS 13 (SPSS Inc., Chicago, IL) using T-test, chi-square, Mann-Withney, and odds ratio with 95% confidence interval.

RESULTS

One hundred eighty women aged 27.48 ± 5.4 (mean ± SD) participated in the study. They participated in two groups of 90 women in each PE (case) group and without PE (control) group. Their demographic and fertility characteristics are compared and summarized in Table 1. The comparison between the two groups of case and control regarding the possible confounding variables, demonstrated no significant differences between them (Table 1).

Six women (6.7%) in the control group and 9 women (10%) in the case group had a history of PE during previous pregnancies which was not significantly different between the two groups (chi-square; $p > 0.05$). The remaining subjects were primiparous women or women without a history of GH or PE during their last pregnancy. In addition, 26 women (28.9%) of in the case group and 23 women (25.6%)

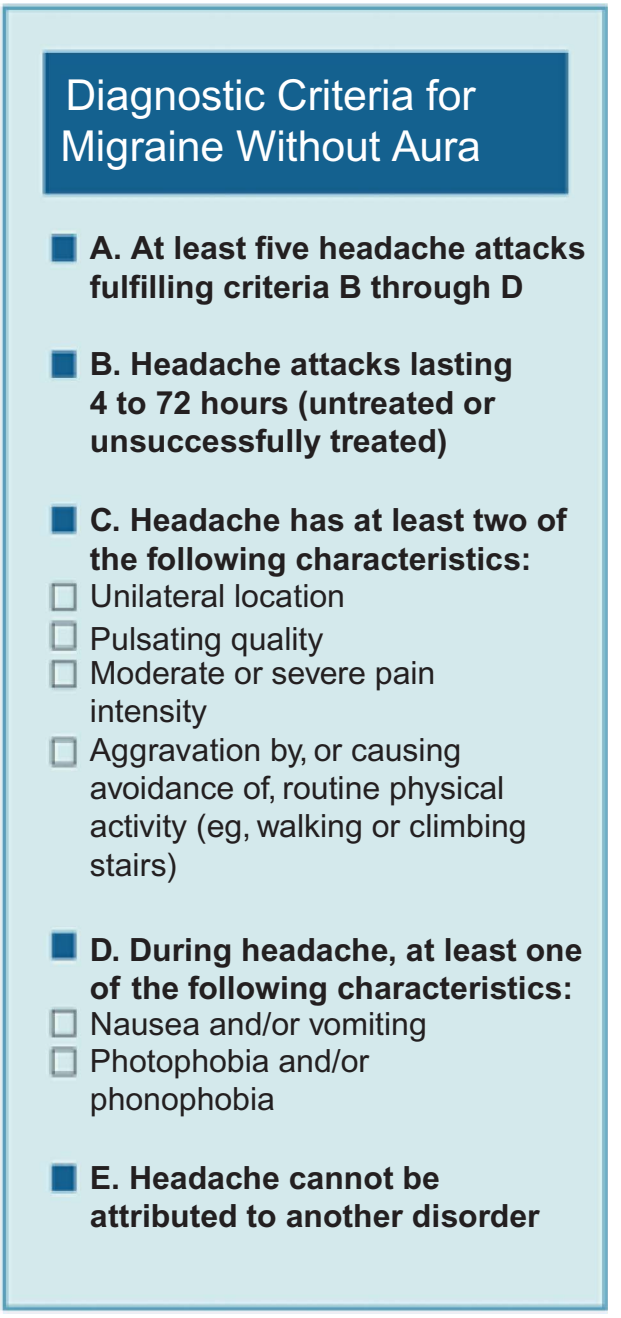

FIGURE 1 The International Classification of Headache Disorders II (ICHD-II) criteria for migraine without aura (13).

in the control group had a family history of hypertension which also was not significantly different between the two groups (chi-square; $p > 0.05$). Eighteen (10%) women were affected by migraine and there were no cases of migraine with aura.

There was a significant difference between the two groups regarding their gestational age at the time of delivery, the weight of their neonate, and the method of their delivery (Table 2).

The comparison between the two groups demonstrated a significant difference in their history of migraine (chi-square; $P < 0.05$). The odds ratio (OR) estimated that there is 2.87 times more history of migraine among the PE group vs. the control group (upper and lower limit of 2.33 and 3.1, respecticely; confidence interval (CI): 95%) (Table 3).

DISCUSSION

This is the first report of an association between migraine and PE in an Asian country. Our findings are consistent with previous reports showing a clear association between migraine and PE and we have extended it to the Iranian population. We used the conventional rigorous NHBPEP (30) criteria for diagnosis and classification of PE as well as ICHD-II (13) criteria for the diagnosis and classification of migraine plus further confirmation of migraine by the neurologist, while most of the previous studies relied on the diagnosis of migraine based on the patients self-report.

The correlation between migraine and an increased risk of PE is attributed to some similarities in pathophysiology of these disorders. The mechanism of migraine and PE are not clearly understood but abnormal reactivity of vascular endothelial cells and the inflammatory release of similar cascades of mediators such as cytokines are believed to cause this association. Abnormal release of cytokines and endothelins are reported in both migraine and PE.

Nitric oxide, oxidative stress, endothelin, arachidonic acid metabolites, renin-angiotensin system, cytokines, angiogenic factors, and metabolic and dietary factors are described as the potential mediators of endothelial dysfunction in PE (31). It is postulated that inadequate remodeling of the uterine spiral arteries in PE leads to focal ischemia and the generation of inflammatory cytokines, such as tumor necrosis factor (TNF alpha) and interleukins (ILs), by the placenta and anything additional (32). Increased levels of IL-6 and IL-8 (33) and elevated levels of TNF-alpha and IL-6 (34) may contribute to the putative endothelial dysfunction of PE. Migraine is also a neurovascular disorder involving cortical depression, neurogenic inflammation, and vasodilation. Various neuropeptides and cytokines have been implicated in the pathophysiology of migraine including calcitonin gene-related peptide, interleukin (IL)-1, IL-6, and tumour necrosis factor (TNF)-alpha (35).

Women with severe PE have a higher median plasma concentration of adiponectin than that of normal pregnant women (36). It is supposed that adiponectin levels are potentially altered during migraine attacks. The anti-inflammatory activities of adiponectin

TABLE 1 The comparison of individual and fertility characteristics of women with PE (the case group) and women without it (the control group) in Kashan hospitals 2007

Characteristics \ Group	Case N = 90	Control N = 90	Statistical Test
Individual			
Age (years); mean ± SD	27.3 ± 5.9	27.66 ± 5.2	T test; p > 0.05
BMI; mean ± SD	28 ± 5.6	26.5 ± 4.6	T test; p > 0.05
Occupation N (%)			
Housewife	87 (96.7)	87 (96.7)	chi square; p > 0.05
Employed	3 (3.3)	3 (3.3)	
Fertility			
Gravida; mean ± SD	2.09 ± 1.3	2.09 ± 1.3	T test; p > 0.05
Parity; mean ± SD	1.8 ± 1.9	1.88 ± 0.9	T test; p > 0.05
Abortion; mean ± SD	0.5 ± 0.2	0.5 ± 0.2	T test; p > 0.05
Unwanted pregnancy; N (%)	19 (21.1)	22 (24.4)	chi square; p > 0.05
Birth space (years); mean ± SD	3.8 ± 4.8	3.9 ± 4.9	Mann-Withney, p > 0.05
Gender of neonate; N (%)			
female	40 (44.4)	43 (47.8)	chi square; p > 0.05
male	50 (55.6)	57 (52.2)	
Oral contraceptive use; N (%)	15 (16.7)	17 (18.9)	chi square; p > 0.05

TABLE 2 The comparison of gestational age at the time of delivery (GA), method of delivery, and weight of neonate of women with PE (case group) and women without it (control group) in Kashan hospitals 2007

Characteristics \ Group	Case N = 90	Control N = 90	Statistical Test
Gestational age at birth (weeks); mean ± SD	37.3 ± 2.6	38.7 ± 1.3	T test; P < 0.01
Method of delivery; N (%)			
Normal vaginal	53 (58)	76 (84.4)	chi square; p < 0.01
Cesarean	37 (42)	14 (15.6)	
Weight of neonate; mean ± SD	2930 ± 690	3330 ± 420	T test; P < 0.01

TABLE 3 The comparison of history of migraine of women with PE (case group) and women without it (control group) in Kashan hospitals 2007

Characteristics \ Group	Case N = 90	Control N = 90	Statistical Test
History of migraine	13 (14.4)	5 (5.6)	chi square; P < 0.05
No history of migraine	77 (85.6)	85 (94.4)	odds ratio: 2.87; p < 0.05
Total	90 (100)	90 (100)	

include inhibition of IL-6 and TNF-induced IL-8 formation, as well as induction of the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist. (35).

Pre-eclampsia is associated with higher circulating and placental endothelin-1 levels, observation that explains, at least in part, vasoconstriction and oxidative stress (37). Endothelins may be the mediators of the vasoconstrictive phase in migraine attacks as well (38).

The rennin-angiotensin system (RAS) is involved in the development of PE, and the presence of the angiotensin II, type I receptor agonistic auto-antibody are frequently reported (39,10). Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers also demonstrate to be effective in the prophylactic

treatment of migraine and it is likely that the RAS has a clinically important role in migraine pathophysiology as well (40).

Platelet sensitivity to prostaglandin E1 inhibition is reduced in PE (41) and platelet insensitivity to prostaglandin E1 was also reported in migraine (42).

Melatonin was demonstrated to be involved in endothelial dysfunction of both migraine and PE. The antioxidative effect of melatonin on the oxidized low-density lipoprotein induced impairment of nitric oxide production in human umbilical artery, which is a cause of endothelial dysfunction in PE (43). Altered melatonin levels in cluster headaches and migraines have also been documented. Melatonin mechanisms are related to headache pathophysiology in many ways, including its anti-inflammatory effect, toxic-free radical scavenging, reduction of pro-inflammatory cytokine upregulation, and nitric oxide synthase activity (44).

Migraine and PE occurrence are both influenced by sex hormones (14,45). The greater incidence of hypertension in men and post-menopausal women compared to premenopausal women has suggested sex hormone differences in vascular function. Activation of sex hormone receptors on the plasma membrane stimulates endothelium-dependent vascular relaxation. Sex hormones also cause endothelium-independent inhibition of vascular smooth muscle contraction (46). Estrogen increases endothelial vasodilator function, promotes angiogenesis, and modulates autonomic function (47).

Migraine is also three times more common in post-pubertal women than in men. Migraine is frequently exacerbated perimenstrually and commonly occurs exclusively at that time (48). It is often benefited by pregnancy and menopause. These improvements have been attributed to the absence of hormone fluctuations. Estrogen withdrawal has been implicated as a mechanism for triggering migraines (49, 14). It has been established that estrogen decreases cerebral vascular tone and increases cerebral blood flow by enhancing endothelial-derived nitric oxide and prostacyclin pathways (50).

Cerebrovascular inflammation is suppressed by estrogen but increased by progesterone. Evidence suggests that sex steroids also modulate blood-brain barrier permeability. Estrogen has important protective effects on cerebral endothelial cells by increasing mitochondrial efficiency, decreasing free radical production, promoting cell survival and stimulating angiogenesis (51). Female sex steroids have an important role in the pathology of migraines by modulating several mediators and/or receptor systems (52).

The results of our study showed that the gestational age at delivery and the neonatal weight of pre-eclamptic group is significantly lower than the control group. In some pre-eclamptic women, the termination of pregnancy is the only available option to prevent further deterioration of the fetus and mother. Fifteen percent of all preterm births are indicated early deliveries for PE (53). In our study, the pre-eclamptic women had a higher rate of cesarean section compared to the control group.

Indeed, patients with PE and those delivering small-for-gestational age (SGA) neonates have higher plasma concentrations of soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) and the soluble form of endoglin (s-Eng), as well as lower plasma concentrations of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) than do patients with normal pregnancies. Otherwise, an imbalance between angiogenic and anti-angiogenic factors has been proposed as central to the pathophysiology of PE (54).

Studies showed similar management for migraine and PE. Asprin as an antiplatelet agents for preventing and treating pre-eclampsia (55) and migraine (56). Magnesium sulfate is the drug of choice to prevent and treat eclampsia (57) and has prophylactic effects on migraines (58).

Several population-based studies have linked migraine and PE, with an increased risk of any ischemic vascular events, including coronary heart disease and ischemic stroke.

Increasing evidence indicates that hypertension in pregnancy is a risk factor for cardiovascular disease (59) and stroke (60). Migraine with aura is associated with an increased risk of ischaemic stroke, angina, and other ischaemic vascular events, including myocardial infarction (61). Potential mechanisms involve shared risk factors, interrelationships between vascular pathologies with migraine (11) and with PE (60).

Migraine has been questioned as one of the risk factors for pre-eclamsia (28). Although most epidemiological studies demonstrate that women suffering from migraines note a significant improvement of their headaches during pregnancy (27.28), frequent reports of a significant association between migraines and PE/GH suggest a history of migraine as a risk factor for PE. It seems that it is time to add a history of migraine to the list of PE risk factors.

It should also be considered that case–control studies are overinvolved by recall bias and also by the fact that headaches are often symptoms of PE and so the PE group may reinforce headache history better than the control group. Further research is necessary to clarify the pathophysiology of both disorders—PE and migraines

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