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The Potential Protective Role of Aspirin Against Migraine in Pregnant Women

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Females are highly predisposed to the occurrence of migraine, a recurrent neurovascular headache disorder. Although migraine improves or disappears during pregnancy, a significant association between migraine and hypertension (i.e., pre-eclampsia) or vascular complications (i.e., stroke) during gestation has been determined. Low-dose aspirin exerts an antithrombotic effect and can improve vascular resistance by regulating endothelial function, which are implicated in the pathogenesis of migraine, pre-eclampsia, and other vascular complications during pregnancy. Low-dose aspirin is widely used prophylactically in the general population who are at higher risk of developing stroke or in pregnant women at higher risk of pre-eclampsia. In this paper we discuss the recent trends in research on the relationship between migraine and pre-eclampsia, an issue of paramount importance in obstetric care, and the potential relationship between migraine and vascular complications in pregnant women. In addition, the potential validity of low-dose aspirin prophylaxis in pregnant women with migraine is explored.

MeSH Keywords: Aspirin • Migraine Disorders • Pre-Eclampsia • Pregnancy • Stroke

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Background

Migraine disorder is a common neurologic disorder in the general population, characterized by headache with severe pulsating one-sided attacks, often accompanied by photophobia and nausea, which can last up to 72 h [1,2]. It has a predilection for females. The lifetime incidence of migraine is 3-fold higher among women than men (prevalence 18% *vs.* 6%, respectively) [3]. In women ages 30–39 years (the central period of childbearing age) the incidence of migraine is 24%. Also, there is a gradual, progressive decline around the average age of menopause [3]. Indeed, ovarian hormone exerts a profound impact on the natural history of migraine [4].

The pathogenesis of migraine involves an incompletely clarified mechanism originating from neural activation in the brainstem, and then release of neuropeptides associated with vasodilation, vascular dysfunction, inflammation, and pain [1,4,5]. It is assumed ovarian hormonal fluctuation triggers common migraine. Estrogens can modulate neuronal excitability and interact with the vascular endothelium of the brain. An association have been found between estrogen and neurotransmitters such as serotonin, which is involved in modulating the pain threshold [6]. In a rodent model, the mRNA levels of tryptophan hydrolase in the trigeminal ganglia were 3-fold higher when associated with elevated estrogen levels compared to phases of the menstrual cycle in which estrogen levels are low [6]. The drop in estrogen levels increases susceptibility to the effects of prostaglandins (PG), the levels of which are 3-fold higher in the central nervous system and endometrium during the last days of the luteal phase [7,8]. Therefore, migraine benefits from the stable ovarian hormonal environment during pregnancy.

Most epidemiological studies have shown that migraine improves or disappears during pregnancy [9]. A systematic review summarized by Negro indicates about one-half to three-fourths of women with migraine experience a marked improvement during pregnancy, with a significant reduction in frequency and intensity of attacks, if not a complete resolution [10]. Despite these observations, recent studies into the medical complications of pregnancy in women with migraine have cast doubts on this assumption. Indeed, several studies have revealed a significant association between migraine and hypertension (i.e., pre-eclampsia), and vascular complications (i.e., stroke) during gestation.

Migraine and Pre-Eclampsia

Pre-eclampsia (PE), a pregnancy-specific syndrome affecting 3–5% of pregnancies, is one of the leading causes of maternal, fetal, and neonatal morbidity and mortality worldwide [11]. PE is a pregnancy-specific disease characterized by *de novo* development of hypertension and proteinuria or end-organ dysfunction after 20 weeks of gestational age [11]. As a multisystem disorder, it can cause cerebrovascular, cardiac, hepatic, hematological, and renal complications in the mother, and even increase the risk of developing cardiovascular disease of women later in life. The complex pathophysiology of pre-eclampsia remains incompletely understood, but it involves abnormal placentation leading to placental hypoxia, imbalance of proangiogenic and antiangiogenic factors, immune dysregulation, and a cascade of cytokine-mediated inflammatory effects resulting in endothelial dysfunction [12].

Although the primary mechanisms of both migraine and pre-eclampsia are poorly understood, both diseases are characterized by altered vasoreactivity and endothelial dysfunction [11–13]. In pregnancy, women with migraine may have poor vascular compensatory mechanisms to deal with pre-eclampsia, which implicates endothelial dysfunction. The hypothesis that women with migraine have a higher incidence of pre-eclampsia has been verified by some epidemiological studies (Table 1).

A correlation between migraine and pre-eclampsia was hypothesized as early as 1959 [14]. A cross-sectional study reported 21.4% of migraine pregnancies (n=221) developed some forms of pre-eclampsia [14]. However, the findings must be interpreted with caution as the diagnosis of both migraine and pre-eclampsia (as toxemia used to be called) was inconsistent with contemporary standards.

A US population-based case-control study analyzing pregnancy-related discharge diagnoses by distinguishing ICD-9 codes from 2000 to 2003 demonstrated 33 956 migraine codes were identified (total 18 345 538 pregnancy-related discharges) [15]. Pre-eclampsia/gestational hypertension codes were associated with migraine codes (OR 2.3, 95% CI 2.1 to 2.5) [15]. Although the study used a population-based sample, the study has obvious limitations related to analyzing ICD-9 codes at discharge from hospital; for instance, some diagnoses of peripartum migraine could have been miscoded or inadvertently listed separately in the setting of pre-eclampsia in which headache is a symptom [15].

In a large case-control study designed to examine the risk of adverse pregnancy outcomes in East Asian women with migraine, Chen et al. identified a total of 4911 women with migraine, together with 24 555 matched women as a comparison cohort [16]. After adjusting for infant sex, parity, maternal age, highest maternal education level, parental age difference, mother's marital status, and family monthly income, as well as hypertension, diabetes, hyperlipidemia, and coronary heart disease, the odds ratio (OR) for pre-eclampsia was 1.34 (95% CI 1.02 to 1.77) [16]. Although, the sample size was relatively

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Table 1. Studies examining the relation between migraine and preeclampsia or pregnancy-induced hypertension.

Author (year)	Study type	Population (N)	Main results
Rotton WN (1959) [14]	Cross-sectional	221	21.4% of migraine pregnancies developed PE
Bushnell CD (2009) [15]	Case-control	33,956 migraine, 18,311,582 controls	OR 2.3 (95% CI 2.1 to 2.5) for PIH/PE
Chen HM (2010) [16]	Case-control	4,911 migraine, 24,555 controls	Adjusted OR 1.34 (95% CI 1.02 to 1.77) for PE
Facchinetti F (2009) [9]	Prospective cohort	270 migraine, 432 controls	Adjusted OR 2.85 (95% CI 1.40 to 5.81) for PIH
Michelle AW (2011) [17]	Prospective cohort	586 migraine, 2,787 controls	OR 1.53 (95% CI 1.09 to 2.16) for PE
Grossman TB (2017) [18]	Retrospective observation	86	21.3% severe migraine developed PE

PIH – pregnancy-induced hypertension; PE – preeclampsia; OR – odds ratio.

large, the sample may not accurately represent the population with migraine due to women diagnosed with migraine by ICD-9-CM code from the National Health Insurance Research Dataset. Also, the diagnostic criteria of PE were not detailed.

Facchinetti et al. conducted a prospective cohort study in 270 cases of migraine (based on ICHD-II) and 432 controls. The OR adjusted for age, family history of hypertension, and smoking habits was 2.85 (95% CI 1.40 to 5.81) for hypertensive disorders in pregnancy (as defined by ACOG 2012 criteria) [9]. The study further clarified the relationship between the course of migraine in pregnancy and onset of hypertensive disorders. Women whose symptoms did not change (OR 1.92, 95% CI 0.71 to 5.19) or worsened (OR 13.65, 95% CI 4.13 to 45.08) showed a higher risk of developing symptoms that either disappeared or improved [9]. However, the study did not perform separate analyses for the risk of PE.

In addition, a prospective cohort study of 3373 pregnant women indicated that migraineurs had 1.53-fold increased odds of having pre-eclampsia (95% CI 1.09 to 2.16) [17]. Additionally, migraineurs who were overweight or obese had 6.10-fold increased odds of pre-eclampsia (95% CI 3.83 to 9.75) as compared with lean non-migraineurs [17].

In a recent retrospectively study, Grossman et al. examined the data of 86 severe migraineurs manifesting in pregnancy requiring emergent treatment who gave birth between 2009 and 2014; patients experiencing severe migraine during pregnancy had high rates of PE 21.3% (95% CI 7.7-24.3). Patients at or above the age of 35 years had a greater chance of having PE (7/16 [43.8%]) compared to those who were younger (15/63 [23.8%]). Although this is the only study focusing on pregnant women with the most severe migraines, this was an observational study with a small sample size [18].

These preliminary results reinforced the idea that PE and migraine share similar pathogenetic mechanisms. Overall, evidence suggests that migraine is an independent risk factor in PE and the risk of PE may sharply rise when combined with other risk factor (e.g., obesity and age).

Migraine and Cardiovascular Disease During Pregnancy

Several case-control and cohort studies, as well as pooled data analyses, indicate that migraine is a risk factor for stroke and other vascular events [19–21]. Stroke is a relatively rare but devastating complication during pregnancy. James et al. conducted a study based on the United States Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality during 2000–2001, showing diagnosis of stroke at a rate of 34.2 per 100 000 deliveries in a total of 2850 pregnancy-related discharges [22]. However, the incidence was roughly 3 times that seen in the general population of young adults [23].

When ischemic stroke was the outcome of interest, migraine was strongly associated with stroke (OR 16.9, CI 9.7–29.5) [22]. A second analysis, performed by Ashley Wabnitz and Cheryl Bushnell, reported an association between increased risk of ischemic stroke and migraine in pregnancy (OR range 7.9–30.7) [24], in which the risk for stroke was 15-fold higher, with odds ratios of 30.7 for ischemic and 9.1 for hemorrhagic stroke.

In addition, evidence demonstrates migraine increases the risk of cardiovascular disease (CVD) (HR 1.5, 95% CI 1.33–1.69) and cardiovascular mortality (HR 1.37, 95% CI 1.02–1.83) [20]. Despite the higher relative risk, the absolute risk of CVD in young women is low except for pregnant women. For instance,

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pregnant women are 4 times more likely to develop venous thromboembolism (DVT) than non-pregnant women, with a standardized incidence ratio of 4.29 (95% CI 3.49–5.22) [25]. Nevertheless, few studies have specifically focused on the risk of pregnancy-related CVD in women with migraine. Bushnell conducted a US population-based case-control study based on the Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality during 2000–2003. The results showed that migraines were associated with nearly a 5-fold increased risk of acute myocardial infraction and heart disease during pregnancy (OR 4.9, 95% CI 1.7–14.2), and an increased risk of thromboembolism such as pulmonary embolism (OR 3.1, 95% CI 1.7–5.6), deep vein thrombosis (OR 2.4, 95% CI 1.3–4.2), and thrombophilia (OR 3.6, 95% CI 2.1–6.1) during pregnancy [15].

Pregnancy is widely thought of as a high-risk factor for stroke or CVD due to hypercoagulability and hemodynamic changes [1]. Researchers hypothesize that the vascular vulnerability and hypercoagulation state of pregnancy may be involved [5]. Migraine can be regarded as an expression of this underlying condition which, when combined with other modifiers of vascular health, can lead to a synergistic increase in CVD risk [1,5]. This hypothesis may explain the multiplicative risk seen in young females with migraine who take oral contraceptives [1,26]. In addition, increased inflammation, thrombogenicity, and altered vasodilatory reaction have been verified in migraine sufferers, and can be seen as markers of dysfunction of the endothelium, which is the inner lining of the blood vessel that normally has vasoprotective properties [1,13].

Aspirin in Pregnancy

It is widely accepted that aspirin plays a positive role in preventing cardiovascular events. As a nonsteroidal anti-inflammatory drug, aspirin prevents cyclooxygenases binding to arachidonic acid, which inhibits the production of prostanoids such as prostacyclins and thromboxane A2 [27]. It can also increase the production of nitric oxide (NO), an endothelial-derived vasodilator, by acetylating endothelial NO synthase [28]. In a recent animal study, aspirin was shown to have a direct vasodilatory effect on rat uterine artery, which is primarily mediated by endothelial cells [29].

There has been limited progress in developing remedies for pre-eclampsia, as the pathogenesis of the disease is not completely understood. The current strategy for management of established pre-eclampsia focuses on balancing of risks to the mother while minimizing the risk of iatrogenic prematurity [11]. To date, pregnancy termination is the only way to eradicate the disease. Therefore, emphasis has been placed on the prevention of pre-eclampsia. For years, low-dose aspirin has been commonly used to prevent or delay the onset of pre-eclampsia [30,31].

It is important to identify women who will benefit from aspirin treatment. Current guidelines recommend the use of clinical history in risk stratification of women [31,32]. The American College of Obstetricians and Gynecologists (ACOG) committee suggests low-dose aspirin (81 mg/day) prophylaxis is recommended and should be initiated at 12–28 weeks of gestation (optimally before 16 weeks) and continued daily until delivery [31]. Low-dose aspirin prophylaxis should be considered for women at high risk of pre-eclampsia or those who have more than 1 of several moderate risk factors for pre-eclampsia [31]. Women at risk of pre-eclampsia are defined based on the presence of 1 or more high-risk factors (history of pre-eclampsia, multifetal gestation, renal disease, autoimmune disease, type 1 or type 2 diabetes, and chronic hypertension) or more than 1 of several moderate risk factors (first pregnancy, maternal age >35 years, a body mass index >30, family history of pre-eclampsia, sociodemographic characteristics, and personal history factors) [31]. Unfortunately, with regard to pregnancy, doctors often ignore that women with migraines have an increasing risk of pre-eclampsia.

Aspirin therapy for stroke prevention has been extensively investigated and shown to reduce the risk of future vascular events; however, its use in pregnancy has been less well researched [33]. In terms of primary prevention of stroke in patients with migraine, aspirin (100 mg/day) reduced the risk of ischemic stroke (RR 0.76; 95% CI, 0.63–0.93), but not other CVDs [34]. However, the findings in the study should be interpreted with caution due to the small number of outcome events in subgroups [34]. Although evidence is insufficient to make clear evidence-based recommendations about stroke prevention in pregnant women, Mayte et al. summarized a practical guide to manage ischemic stroke during pregnancy, and suggested that aspirin (50–150 mg/day), which is well-tolerated during pregnancy, could be considered for women with higher risk of stroke, including cardioembolism, migraine, and coagulation disorders [35].

Although national guidelines recommend that women at risk of developing pre-eclampsia should be advised to take aspirin daily, the optimal timing and dose of the initiation of aspirin for pre-eclampsia prevention remain controversial [31,36]. Recent studies show that prophylaxis with 100–150 mg of aspirin given before 14–16 weeks can significantly reduce pre-eclampsia rates and may improve pregnancy outcome [30,37]. A meta-analysis conducted by Bujold et al. demonstrated that commencing low-dose aspirin before 16 weeks of gestation significantly decreased the rate of pre-eclampsia (RR 0.47, 95% CI 0.34–0.65) [38]. Although most centers use aspirin 75–100 mg daily, there has been a shift towards using a dose of greater

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than 100 mg daily based on more recent studies. A large multicenter randomized trial showed that aspirin (150 mg per day) from 11–14 weeks to 36 weeks of gestation reduced the risks of preterm pre-eclampsia [30]. Of particular note, a recent meta-analysis reported aspirin at a daily dose greater than or equal to 100 mg for the prevention of pre-eclampsia that was initiated at ≤16 weeks can reduce the risk of placental abruption or antepartum hemorrhage [37]. However, there is a need for more stronger evidence to support the benefits and safe use of aspirin over 100 mg daily before 16 weeks of gestation in the prevention of pre-eclampsia [30,39].

In general, aspirin is typically discontinued after terminating pregnancy. The Hale lactation rating of aspirin is L3 [40]. It is reported aspirin is associated with Reye's syndrome in infants and potential adverse effects on infant's platelet function [40]. Whether continued aspirin use after pregnancy is beneficial in women with a history of pre-eclampsia remains controversial and is rarely discussed. A large cohort in the US population raises the possibility that primary preventive treatment with aspirin after a pregnancy complicated by hypertensive disorders of pregnancy might reduce future stroke risk in this population [41]. Starting low-dose aspirin therapy in post-partum women with migraine also warrants comprehensive investigation.

Conclusions

Although pregnancy is a time of relative well-being for women with migraine, as headaches improve, migraine sufferers may be exposed to additional clinical risks, such as pre-eclampsia, stroke or thromboembolic events. Low-dose aspirin prophylaxis appears to have a protective role in decreasing pregnancy complications. It is of great importance to verify the validity of low-dose aspirin prophylaxis in pregnant women with migraine as vascular homeostasis and to elucidate the antithrombotic effects of aspirin use. In practice, randomized controlled trials could be conducted to evaluate the benefits of the starting low-dose aspirin in pregnant women with migraine. An animal model of migraine could be used to reveal the underling pathogenesis of both migraine and pre-eclampsia, as well as the mechanism of action of aspirin. Simple, inexpensive primary preventive interventions could have major consequences in this high-risk group.

Conflicts of interest

None.

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