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G. Allais • I. Castagnoli Gabellari • G. Airola • P. Schiapparelli • M.G. Terzi • O. Mana • C. Benedetto

Is migraine a risk factor in pregnancy?

Abstract Most epidemiological studies demonstrate that women suffering from migraine note significant improvement of their headaches during pregnancy. It is generally supposed, by both headache specialists and gynaecologists, that migraine does not involve any risk to the mother or the foetus. Specific investigations of the medical complications of pregnancy in migrainous women, however, have recently cast doubt on this assumption. Most studies, indeed, have revealed a significant association between migraine and hypertension in pregnancy (i.e., preeclampsia and gestational hypertension). Migraine has also been recently postulated as one of the major risk factors for stroke during pregnancy and the puerperium. There is thus an urgent need for prospective studies of large numbers of pregnant women to determine the real existence and extent of the risks posed by migraine during pregnancy.

Key words Gestational hypertension • Migraine • Preeclampsia • Pregnancy • Thromboembolic risk

G. Allais (✉) • I. Castagnoli Gabellari • G. Airola • P. Schiapparelli
M.G. Terzi • O. Mana • C. Benedetto
Women's Headache Center
Department of Gynecology and Obstetrics
University of Turin
Via Ventimiglia 3, I-10126 Turin, Italy
e-mail: gb.allais@tiscali.it

Introduction

Migraine is one of the most common neurological disorders in adult women [1] with a female/male prevalence ratio of 3–4:1 [2]. According to the American Migraine Prevalence and Prevention (AMPP) study, this prevalence rises from 4% before puberty to a peak of 25% in women during their childbearing years, with a decrease after menopause [2]. Migraine occurrence is influenced by sex hormone changes during the menstrual cycle and its attacks are often perimenstrual.

Migraine in pregnancy: clinical aspects

Most epidemiological studies demonstrate that migrainous women note significant and increasing improvement of their headaches during pregnancy [1] from the first to the third trimester [3]. Migraine had improved by the third trimester in 87% of 47 women prospectively studied by Sances et al. [4], whereas Marcus et al. found that women with headaches that persist unchanged in the second trimester are less likely to improve thereafter [5]. Improvement seems to be more likely if migraine is without aura and menstrually related, and when its onset is linked to the menarche [6].

These improvements have been attributed to the absence of hormone fluctuations [7], and/or to analgesic effects of β-endorphins, which often increase in pregnancy [1, 8]. However, in some women (i.e., in those suffering from migraine with aura (MA)), migraine may worsen during pregnancy [9]: Granella et al. reported worsening of migraine in 4%–8% of pregnant women, most of whom had MA [6]. A few women experience migraine for the first time during pregnancy [6, 10]. The most recent study [11] found that only 1.9% of pregnant women developed migrainous symptoms *de novo*: here, however, especially if headache is associated with other neurological symptoms,

the possibility of serious intracranial disorders must first be ruled out.

Headache specialists tend to reassure their patients that migraine does not involve any risk to the mother or the foetus; moreover, gynaecologists do not equate it with the risk factors represented by maternal age, obesity, diabetes etc.

Specific investigations of the medical complications of pregnancy in migrainous women, however, have recently cast doubt on these assumptions.

Migraine and hypertension in pregnancy

Preeclampsia (PE) is a pregnancy-specific syndrome that usually occurs after 20 weeks of gestation. It presents as *de novo* hypertension (systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg) on two occasions, 6 h apart, accompanied by new-onset proteinuria defined as ≥300 mg/24 h. PE is usually considered severe if one or more of the following criteria are present: blood pressure 160/110 mmHg or higher, 24-h proteinuria 5 g or higher, oliguria of less than 500 ml in 24 h, cerebral or visual disturbances, pulmonary oedema or cyanosis, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia or foetal growth restriction (birth-weight <10th percentile). Eclampsia occurs when PE progresses to a life-threatening convulsive phase. Gestational hypertension (GH) is defined as *de novo* hypertension arising after 20 weeks of gestation and is distinguished from PE by the absence of proteinuria [12].

The primary mechanism of both migraine and PE is uncertain. Both conditions, however, are characterised by altered vasoreactivity and abnormal platelet behaviour [13, 14] and they may share a common aetiology.

Nowadays 11 studies that investigated the clinical association between migraine and PE are available in the literature. In 1959, Rotton et al. found that 21.4% of 221 pregnant migrainous women had some form of PE, diagnosed if at least two of the following criteria recurred: hypertension, albuminuria and oedema. Their PE was significantly more frequent than expected and was more severe, with a much greater incidence of eclampsia. This picture was linked to worsening of headache during pregnancy [15]. A subsequent comparison of 24 women with severe PE with 48 controls showed that headaches occurring before pregnancy were significantly more common in the PE group (54% *vs*. 17%). Severe PE was diagnosed if patients met the following criteria: increase in systolic and diastolic pressure by at least 30 and 15 mmHg respectively, antenatal systolic and diastolic pressure ≥140 and 90 mmHg respectively, persistent proteinuria ≥1 g/l or ≥1 g/24 h. "Severe headaches", defined as headaches accompanied by nausea, vomiting or visual disturbances, were present in the prior history of 33% preeclamptic women *vs*. 6% of controls [16]. Marcoux et al. assessed the relationship between a history of migraine (ascertained after delivery) and the risk of PE or GH. A total of 152 women with PE and 254 with GH were compared to 505 controls. Migraine was reported by 16% of the preeclamptic women, 12% of women with GH and 8% of the controls. The ORs were 2.44 (95% CI, 1.42–4.20) and 1.7 (95% CI, 1.02–2.85) for PE and GH respectively [17].

A prospective analysis by Chen and Leviton [18] identified 485 pregnant women with preexisting migraine: 21% developed PE, with an almost 10-fold increased incidence compared to the general population. Their "mild PE" category, however, comprised pictures that subsequently were recognised as characteristic of GH and not PE.

In a large case-control study of the relationship between migraine and stroke in 1027 young women, it was shown that both women with stroke (27%) and controls (16.7%) who had a self-reported history of migraine were more likely to develop hypertension in pregnancy compared to women with no migraine ($p<0.05$) [19].

Results from the Genetic Epidemiology of Migraine Study showed that women with migraine diagnosed according to the IHS criteria [20] were significantly more likely to report a history of GH after adjusting for age, socioeconomic status, smoking and alcohol, when compared to women without migraine: OR 1.63 (95% CI, 1.2–2.1) [21].

Facchinetti et al. [14] enrolled 75 women with PE and 75 women with normal pregnancies in a case-control study. Headache was significantly more prevalent in the PE group than in the control group (62.7% *vs*. 25.4%) with an OR of 4.95 (95% CI, 2.47–9.92), particularly migraine without aura (36% *vs*. 10.7%), while episodic tension-type headache was equally distributed. Headache was significantly more prevalent in severe (75%) as opposed to moderate (38.8%) PE patients with an OR of 5.63 (95% CI, 1.97–16.03).

Similarly, in a case-control study of 244 women with PE and 470 normotensive women, Adeney et al. [22] found a 1.8-fold increased risk of PE in women with a history of diagnosed migraine (95% CI, 1.1–2.7); the same risk increased to 12-fold in overweight migrainous women (95% CI, 5.9–25.7). Lastly, Bánhidy et al. [23] revised a population-large data set of newborn infants to evaluate pregnancy complications of mothers with migraine. They found that pregnant women with severe migraine had a higher prevalence of PE as compared with controls (11.4% *vs*. 8.4%), with a prevalence OR of 1.4 (95% CI, 1.1–1.8).

Only two studies reported no association between migraine and medical complications during gestation. Wainscott et al. [24] did not note any significant difference in pregnancy outcomes between 450 women with migraine and 136 nonmigrainous women. The incidence of self-reported PE (undefined) was 18% in both groups and the risk of miscarriage and birth defects was also similar. Mattson, too, found no significant age-adjusted lifetime risk of migraine with or without aura according to pregnancy complications such as self-reported swollen feet, arterial hypertension and proteinuria [25].

Migraine and thromboembolism

Pregnancy is associated with a variety of thromboembolic disorders, e.g., deep veinous thrombosis and pulmonary embolism. In some respects, pregnancy may be considered a hypercoagulable state: platelet hyperaggregability and decreased fibrinolysis are present, while the levels of clotting proteins (fibrinogen and factors V, VII, VIII, IX, X and XII) increase during the third trimester, together with increased resistance to protein C with decreased protein C inhibitory activity [26].

Pregnant women are 4 times more likely to develop venous thromboembolism (VT) than women who are not, with a standardised incidence ratio of 4.29 (95% CI, 3.49–5.22) [27]. Thrombophilia displays the highest association with a significantly increased risk of VT (OR 51.8; 95% CI, 38.7–69.2) [28]. Although venous thromboembolic events are 4 times more common than arterial events [28], and VT is an important complication during pregnancy and the postpartum period, the risk of mortality is 30% higher for stroke than for VT (1.4 compared with 1.1 per 100,000 deliveries) [29] and attention should be directed to this risk factor during pregnancy. Many studies have reported an increased risk of stroke in pregnant women [30, 31]. Migraine, too, particularly MA, is considered an independent risk factor for ischaemic stroke, particularly among young women [32]. Earlier studies have suggested an association between migraine and genetic abnormalities of coagulation factors, which play an important role in stroke pathogenesis. The mechanisms implicated are: factor V Leiden mutation; factor II G20210A mutation; genetically determined deficiencies of antithrombin, protein S and protein C; hyperhomocysteinaemia; methylenetetrahydrofolate reductase C677T or A1298C mutations [33, 34].

Nevertheless, few studies have specifically focused on the risk of pregnancy-related stroke in migrainous women. James et al. [35] reviewed data from the Nationwide Inpatient Sample relative to pregnancy-related discharges. They found that the overall risk of pregnancy-related stroke was 34.2 per 100,000 deliveries. The strongest associations for stroke were migraine, with an OR of 16.9 (95% CI, 9.7–29.5) and thrombophilia, with an OR of 16.0 (95% CI, 9.4–27.2). They also found that complications of pregnancy, such as severe PE and GH, were significant risk factors for pregnancy-related stroke (OR 4.4; C.I. 95%, 3.6–5.4).

Conclusions

Pregnancy is a time of relative well-being for migrainous women and their headaches usually improve. They may, however, be more exposed to some clinical risks, such as hypertension or a thromboembolic event. Recent retrospective and other studies indicate that both headache specialists and gynaecologists should devote greater attention to these patients. There is thus an urgent need for prospective studies of large numbers of pregnant women to determine the real existence and extent of the risks posed by migraine during pregnancy.

References

1. MacGregor A (ed) (1999) Migraine in women. Martin Dunitz Ltd, London, UK
2. Lipton RB, Bigal ME, Diamond M et al (2007) Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 68:343–349
3. Passchier J, Kaminsky MM, Paarlberg KM, van Geijn HP (1996) Stress during pregnancy is unrelated to headache change in migraineurs. Headache 36:189
4. Sances G, Granella F, Nappi RE et al (2003) Course of migraine during pregnancy and postpartum: a prospective study. Cephalalgia 23:197–205
5. Marcus DA, Scharff L, Turk D (1999) Longitudinal prospective study of headache during pregnancy and postpartum. Headache 39:625–632
6. Granella F, Sances G, Zanferrini C et al (1993) Migraine without aura and reproductive life events: a clinical epidemiological study in 1300 women. Headache 33:385–389
7. Silberstein SD (1995) Migraine and women. The link between headache and hormones. Postgrad Med 97:147–153
8. Genazzani AR, Petraglia F, Facchinetti F (1987) Opioids and reproduction. In: Genazzani AR, Volpe A, Facchinetti F (eds) Gynecological endocrinology. Parthenon Publishing, Lancs, pp 43–45
9. Silberstein SD, Merriam GR (1991) Estrogens, progestins, and headaches. Neurology 41:775–793
10. Chancellor AM, Wroe SJ, Cull RE (1990) Migraine occurring for the first time in pregnancy. Headache 30:224–227
11. Ertresvåg JM, Zwart JA, Helde G et al (2005) Headache and transient focal neurological symptoms during pregnancy, a prospective cohort. Acta Neurol Scand 111:233–237
12. ACOG Committee on Practice Bulletins – Obstetrics (2002) ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Obstet Gynecol 99:159–167
13. Adeney KL, Williams MA (2006) Migraine headaches and preeclampsia: an epidemiologic review. Headache 46:794–803
14. Facchinetti F, Allais G, D'Amico R et al (2004) The relationship between headache and preeclampsia: a case-control study. Eur J Obstet Gynecol Reprod Biol 121:143–148
15. Rotton WN, Sachtleben MF, Friedman EA (1959) Migraine and eclampsia. Obstet Gynecol 14:322–330
16. Moore MP, Redman CWG (1983) Case-control study of severe pre-eclampsia of early onset. Br Med J (Clin Res Ed) 287:580–583
17. Marcoux S, Berube S, Brisson J, Fabia J (1992) History of migraine and risk of pregnancy-induced hypertension. Epidemiology 3:53–56
18. Chen TC, Leviton A (1994) Headache recurrence in pregnant women with migraine. Headache 34:107–110
19. Chang CL, Donaghy M, Poulter N, and The World Health

Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception (1999) Migraine and stroke in young women: a case-control study. BMJ 318:13–18
20. Headache Classification Subcommittee of the International Headache Society (IHS) (2004) The International Classification of Headache Disorders: 2nd edn. Cephalalgia 24[Suppl 1]:9–169
21. Scher AI, Terwindt GM, Picavet HSJ et al (2005) Cardiovascular risk factors and migraine: the GEM population-based study. Neurology 64:614–620
22. Adeney KL, Williams MA, Miller RS et al (2005) Risk of preeclampsia in relation to maternal history of migraine headaches. J Matern Fetal Neonatal Med 18:167–172
23. Bánhidy F, Ács N, Horváth-Puhó, Czeizel AE (2006) Pregnancy complications and delivery outcomes in pregnant women with severe migraine. Eur J Obstet Gynecol, DOI:10.1016/j.ejogrb.2006.08.025
24. Wainscott G, Sullivan FM, Volans GN, Wilkinson M (1978) The outcome of pregnancy in women suffering from migraine. Postgrad Med J 54:98–102
25. Mattson P (2003) Hormonal factors in migraine: a population-based study of women aged 40 to 74 years. Headache 43:27–35
26. Benedetto C, Marozio L, Tavella AM et al (2002) Response to activated protein C decreases throughout pregnancy. Acta Obstet Gynecol Scand 81:1028–1032
27. Heit J, Kobbervig C, James A et al (2005) Trends in the incidence of deep vein thrombosis and pulmonary embolism during pregnancy or the puerperium: a 30-year population-based study. Ann Intern Med 143:697–706
28. James AH, Jamison MG, Brancazio LR, Myers ER (2006) Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. Am J Obstet Gynecol 194:1311–1315
29. James A, Brancazio L, Jamison M, Myers E (2004) Peripartum thromboembolism in the United States 2000–2001: incidence, mortality and risk factors. Am J Obstet Gynecol 191:90S
30. Kittner SJ, Stern BJ, Feeser BR et al (1996) Pregnancy and the risk of stroke. N Engl J Med 335:768–774
31. Wiebers DO, Whisnant JP (1985) The incidence of stroke among pregnant women in Rochester, Minn, 1955 through 1979. JAMA 254:3055–3057
32. Tietjen GE (2000) The relationship of migraine and stroke. Neuroepidemiology 19:13–19
33. D'Amico D, Moschiano F, Leone M et al (1998) Genetic abnormalities of the protein C system: shared risk factors in young adults with migraine with aura and with ischemic stroke? Cephalalgia 18:618–621
34. Crassard I, Conard J, Bousser MG (2001) Migraine and hemostasis. Cephalalgia 21:630–636
35. James AH, Bushnell CD, Jamison M, Myers ER (2005) Incidence and risk factor for stroke in pregnancy and the puerperium. Obstet Gynecol 106:509–516