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Headache and adverse pregnancy outcomes: a prospective study

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ABSTRACT

Objective: To investigate the association between headache, namely migraine and tension-type headache, and adverse pregnancy outcome.

Study design: Prospective cohort study conducted in three tertiary care centres in Italy: 376 pregnant women suffering from headache and 326 non-headache pregnant women as controls were recruited. The diagnosis of headache was made at the beginning of pregnancy, according to the criteria of the International Classification of Headache Disorders (ICHD-II). Women were followed up until delivery, and gestational age at delivery, mode of delivery, indications for operative delivery or caesarean section, birth weight, and centile of neonatal weight at birth were carefully recorded. Main outcome measures of the study were: preterm delivery, newborns small for gestational age, and foetal losses. Odds ratios and 95% confidence intervals were calculated.

Results: The incidence of preterm delivery (Adj OR, 95% CI 2.74, 1.27–5.91) was significantly higher in women suffering from headache than in controls. There was no statistically significant difference in small for gestational age newborns between the groups. Fewer women in the headache group had preterm elective caesarean section or induction of labour, than did controls, indicating a higher chance of spontaneous preterm delivery. Multivariate analysis showed that the association between headache, either migraine or tension-type, and adverse perinatal outcomes was statistically significant regardless of pre-eclampsia.

Conclusions: Women with headache should be considered at risk for adverse perinatal outcomes and should, therefore, be included in a high-risk pregnancy protocol of care throughout pregnancy.

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1. Introduction

Headache is one of the most frequent reasons for referral to a neurology outpatient department [1]. Most headache types have a female predominance and a peak incidence age in the second and third decades of life [2,3]. This age range corresponds to the childbearing years for women, thus the association of headache and pregnancy is quite frequent. Data are available as to the effect of pregnancy on headache and in particular on migraine, which has been reported to improve during pregnancy in a high percentage of patients [4–7]. The improvement of tension-type headache (TTH) is less evident, with some studies even reporting opposite results [6,8,9].

To date, few studies have dealt with the impact of headache on pregnancy outcome. Although the mechanisms are not yet fully understood, there seems to be an association between migraine and the risk of pre-eclampsia [10,11]. In a large prospective study [12] we recently observed that the risk of developing hypertension in pregnancy or pre-eclampsia was significantly higher in migraineurs (9.1%) compared to non-migraineurs (3.1%) (OR 2.85, 95% CI 1.40–5.81). Women with migraine also showed a tendency to increased risk of low birth weight infants [12]. Very little information is available as to the effect of headache on perinatal outcomes, such as preterm delivery, low birth weight and/or intrauterine foetal growth restriction. In the limited number of studies that have evaluated pregnancy outcomes in migraineurs, the majority reported no increase in the incidence of poor outcomes such as preterm labour, low birth weight and/or congenital anomalies [8,11]. A recent study suggests that patients with migraine were at higher risk of pre-eclampsia, preterm birth and caesarean section compared to unaffected mothers [13].

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However, most data on perinatal outcome were obtained from retrospective studies and were not adjusted for pregnancy complications or other factors with a potential negative effect on pregnancy outcome, and this may well represent a selection bias. Moreover, most studies have dealt with migraine and pregnancy, whilst very few reports have been published on the effect of TTH on perinatal outcomes.

This scarcity of data prompted us to carry out a prospective, multicentre, cohort study in an attempt to determine whether the presence of headache, either migraine or tension-type, may be an independent adverse risk factor for perinatal outcome.

2. Materials and methods

Women attending antenatal booking at three maternity units in Italy (Departments of Obstetrics and Gynaecology, University of Torino and Modena, and the Research Centre for Reproductive Medicine, the University of Pavia) were enrolled into a cohort prospective study aimed at the evaluation of the incidence of pre-eclampsia in migraineur women.

When booking, at a gestational age of 11–16 weeks, the women were interviewed by three researchers who had previously been trained in headache diagnosis according to the criteria of the International Classification of Headache Disorders (ICHD-II) [14]. A semistructured questionnaire was also used to facilitate the interview and collection of data. Details of the questionnaire have been previously reported [9]. A clinical examination was made along with an ultrasound scan, during the enrolment interview, to confirm gestational age, and the woman's age, years of education, family history, last menstrual date, parity, and smoking habits were recorded. Only Caucasian women with singleton pregnancies were included. Chronic hypertension, pre-existing diabetes and any other systemic disorders that might have a negative effect on pregnancy outcome were considered exclusion criteria.

The diagnosis of headache type, i.e. migraine or TTH, was based on the ICHD-II criteria. Attacks and/or headache lacking one of the features required to fulfil the criteria for migraine with or without aura, or TTH were coded as "probable migraine" or "probable TTH". In some cases, the diagnosis of headache type had already been made and was therefore confirmed at enrolment. All the diagnoses were independently reviewed by a senior researcher (G.A.).

A total of 11/753 women interviewed did not meet the inclusion criteria. Seven women chose to terminate the pregnancy after prenatal diagnosis of chromosomal abnormalities and 33 were lost to follow-up. Consequently, data were available for 702 women who had follow-up throughout their pregnancy. Three hundred and seventy-six were suffering from headache and 326 were not and were therefore taken as controls. Data as to the incidence of pre-eclampsia in pregnant women suffering from migraine in the same cohort have been previously reported [12].

The primary objective of the study was to assess whether the pregnant women with headache had worse perinatal outcomes than did the controls. The information on outcomes was directly recorded at the time of delivery, or immediately afterwards, through medical note revision. Gestational age at delivery, mode of delivery, indications for operative delivery or caesarean section, birth weight, and centile of weight at birth were carefully recorded. The following primary outcomes were considered: (1) preterm delivery, defined as a birth occurring before 37 completed weeks of gestation, and (2) newborns that were small for gestational age (SGA), defined as a newborns whose weight was below the 10th centile for gestational age at birth in the absence of foetal malformations, chromosomal abnormalities, recent cytomegalovirus infection and/or maternal substance or alcohol abuse [15].

New onset of gestational hypertension (GH) and preeclampsia (PE) was carefully recorded. In agreement with the criteria

established by the American College of Obstetricians and Gynaecologists [16], diagnosis of GH was made in the presence of new onset hypertension (blood pressure ≥ 140 and/or 90 mmHg in two measurements at least 6 h apart) without proteinuria after the 20th week of gestation in a previously normotensive woman, that resolved within 12 weeks after delivery. PE was diagnosed if hypertension, associated with significant proteinuria (≥ 300 mg/24 h), occurred after 20 weeks' gestation in a previously normotensive and non-proteinuric woman and resolved within 12 weeks after delivery.

Details of any changes in headache patterns and drug intake, e.g. triptans, were also collected. Headache sufferers were instructed to take note of any headache attacks and analgesic use in a personal diary. All data were checked at the post-partum interview, which was done 6–12 weeks after delivery, either directly or by telephone.

The protocol was approved by the local Ethics Committees and written informed consent was obtained from each subject before enrolment.

So as to perform a power analysis of the study, we considered that the prevalence of recurrent headaches in women of reproductive age to be around 54% [17] and that of preterm delivery in the general population around 10% [18]. Therefore, we calculated that our sample size had a power of 80% to detect an odds ratio of 2.0 at the 5% level for preterm delivery between groups. Data were downloaded in the SPSS 12.0 software (Statistical Package for the Social Sciences, Chicago, US). Association between headaches and perinatal outcomes was expressed as odds ratios (OR) and 95% confidence intervals (CIs) were calculated by the logistic regression model in SPSS. The *p*-values were also reported, and considered statistically significant when <0.05 . A multivariate logistic regression analysis was carried out to provide adjusted OR estimates so as to account for possible differences in the distribution of potential confounding variables, with and without headache, in particular that of gestational hypertension and pre-eclampsia. Only those covariates that had a *p*-value of <0.1 at the univariate analysis were taken into consideration in the multivariate analysis.

3. Results

Three hundred and seventy-six of the 702 women recruited into the study were diagnosed as headache sufferers (53.5%), and the 326 that were not diagnosed made up the controls. Six headache patients and seven controls had spontaneous miscarriages after enrolment. There were two foetal deaths in the headache group (one following placental abruption and one of unknown cause) and one early neonatal death (of a severely preterm newborn). There were one foetal death of undetermined cause and two early neonatal deaths following severe preterm delivery in the control group. There was no statistically significant difference in foetal/neonatal losses between groups.

After exclusion of subjects with foetal losses, 367 headache patients and 316 controls delivered a viable newborn and were then considered for statistical analysis.

Migraine was diagnosed in 264 women (38.6%), 180/264 without aura, 35 with aura, and the remaining 49 reported a "probable" migraine. A diagnosis of TTH was made in 103 subjects (15.1%), with 11/103 reporting a "probable" TTH.

Women with or without headache did not differ in terms of age distribution, years of education, body mass index (BMI), smoking habit, or family history of GH/PE, whereas a family history of hypertension was slightly but statistically significantly more frequent in headache women than in controls (Table 1).

The incidence of preterm delivery (<37 weeks' gestation) was significantly higher in patients suffering from headache than in

Table 1
Baseline characteristics of women with or without headache.

Variables	No headache N: 316 n (%)	Headache N: 367 n (%)	OR (95% CI)	p
Age (years)				
≤25	24 (7.6)	24 (6.5)	Reference	0.40
26–34	235 (74.4)	262 (71.4)	1.12 (0.62–2.02)	
≥35	57 (18.0)	81 (22.1)	1.42 (0.74–2.75)	
Education (years)				
<8	75 (23.7)	81 (22.1)	Reference	0.84
9–13	167 (52.9)	195 (53.1)	1.08 (0.74–1.58)	
>13	74 (23.4)	91 (24.8)	1.14 (0.73–1.77)	
BMI				
20–24.9	145 (45.9)	171 (46.6)	Reference	0.48
<20	68 (21.5)	86 (23.4)	1.07 (0.73–1.58)	
25–29.9	43 (13.6)	56 (15.3)	1.10 (0.70–1.74)	
≥30	60 (19.0)	54 (14.7)	0.76 (0.50–1.17)	
Parity				
Nulliparous	184 (58.2)	210 (57.2)	Reference	0.92
Parous	132 (41.8)	157 (42.8)	0.99 (0.73–1.34)	
Family history of GH/PE				
No	268 (84.8)	324 (88.3)	Reference	0.36
Yes	10 (3.2)	11 (3.0)	0.91 (0.38–1.15)	
Not known	38 (12.0)	32 (8.7)	0.70 (0.42–1.15)	
Family history of hypertension				
No	170 (53.8)	166 (45.2)	Reference	0.03
Yes	111 (35.1)	165 (45.0)	1.52 (1.10–2.10)	
Not known	35 (11.1)	36 (9.8)	1.11 (0.63–1.76)	
Smoking habit				
No	234 (74.1)	258 (70.3)	Reference	0.27
Yes	82 (25.9)	109 (29.7)	1.21 (0.86–1.69)	

BMI, body mass index.

GH, gestational hypertension.

PE, preeclampsia.

controls (Table 2). Seven newborns (1.9%) were delivered below 34 completed weeks of gestation in the headache group and 6/367 (1.6%) weighed less than 2000 g. The incidence of preterm rupture of the membranes was similar for both groups. Amongst women who delivered preterm, 87.5% of the non-headache group had elective caesarean section or induction of labour. Amongst headache subjects, a lower proportion of subjects (77.7%) underwent preterm elective caesarean section or induction of labour, indicating a higher chance of spontaneous preterm delivery. The difference, however, was not statistically significant. The indications for elective preterm delivery were similar between the groups. There was no difference between the groups in the prevalence of prior preterm delivery. In this regard, it is possible that the higher proportion of nulliparous and the very high rate of indicated preterm delivery in both groups can mask the effect of prior preterm delivery on the risk of recurrence in the index pregnancy. There was a higher, although not significant, incidence of caesarean sections and vaginal assisted deliveries in the headache group than in controls (37.1% vs 33.5%); these rates

Table 2
Results according to perinatal outcomes.

Variables	No headache N: 316 n (%)	Headache N: 367 n (%)	OR (95% CI)	Adjusted ^a OR (95% CI)
Preterm delivery (<37 weeks)				
No	307 (97.2)	339 (92.4)	Reference	Reference
Yes	9 (2.8)	28 (7.6)	2.82 (1.31–6.07)	2.74 (1.27–5.91)
SGA (<10th centile)				
No	304 (96.2)	353 (96.2)	Reference	Reference
Yes	12 (3.8)	14 (3.8)	1.01 (0.46–2.21)	1.00 (0.46–2.20)

SGA, small for gestational age.

^a Adjusted for family history of hypertension and for occurrence of GH/PE.

are similar to the average rate of caesarean section in our departments for 2010 (34%).

A separate analysis was performed for the two subgroups, as the pathophysiological aspects of migraine and TTH differ (Table 3). The incidence of preterm delivery was higher in patients suffering from migraine than in controls, as was the case in the whole group of headache patients. In patients with TTH we observed a significantly higher incidence of preterm delivery together with a high incidence of small for gestational age newborns which, however, did not reach the statistical significance.

The analysis performed according to subtypes of migraine (with or without aura and “probable” migraine) and of TTH (pure or “probable” TTH) confirmed the results and revealed no statistically significant differences amongst headache subtypes in terms of perinatal outcome.

The incidence of GH/PE was significantly higher in headache patients (10.4%) than in non-headache controls (2.3%; OR 4.60, 95% CI 1.99–10.68). As previously reported (12), GH/PE occurred more frequently in patients with migraine (12.6%; OR 5.55, 95% CI 2.34–13.12 vs controls) than in those with TTH (5.7%; OR 2.73, 95% CI 0.89–8.32 vs controls).

The multivariate analysis showed that the association between headache, either migraine or tension-type, and adverse perinatal outcomes remained statistically significant after adjusting for family history of hypertension and occurrence of GH/PE (Tables 2 and 3).

4. Comment

This prospective cohort study shows that pregnant women suffering from headache have a statistically significantly higher incidence of preterm delivery and a higher, although not significantly, incidence of SGA infants than do non-headache subjects. Moreover, it was observed that both migraine and TTH are risk factors for preterm delivery and that headache patients have a higher, though not statistically significant, percentage of spontaneous preterm labour than do non-headache women. This finding is in disagreement with Banhidly et al. [11], who reported that although severe maternal migraine and its related drug treatment may increase the occurrence of pre-eclampsia and severe nausea/vomiting during pregnancy, it is not associated with unfavourable delivery outcomes, such as preterm birth and/or low birth weight. However, Banhidly et al.’s study was retrospective and the size of the two groups differed greatly (713 women with migraine and 37,438 controls), which may well represent a selection bias. We have observed that both migraine and TTH are related to preterm delivery, and, to the best of our knowledge, this is the first study dealing with the effect of TTH on pregnancy outcomes. As the drugs usually administered to treat TTH and/or migraine attacks are often different, it is unlikely that the effect of the two headache types is drug related. It has been hypothesized that the use of sumatriptan may influence perinatal outcome [19].

Table 3
Results according to headache subtypes.

Variables	No headache N: 316 n (%)	Migraine N: 264 n (%)	OR (95% CI)	Adjusted ^a OR (95% CI)	TTH N: 103 n (%)	OR (95% CI)	Adjusted ^a OR (95% CI)
Preterm delivery (<37 weeks)							
No	307 (97.2)	245 (92.8)	Reference	Reference	94 (91.3)	Reference	Reference
Yes	9 (2.8)	19 (7.1)	2.65 (1.18–5.95)	2.55 (1.13–5.75)	9 (8.7)	3.27 (1.26–8.47)	3.22 (1.22–8.20)
SGA (<10th centile)							
No	304 (96.2)	255 (96.5)	Reference	Reference	98 (95.1)	Reference	Reference
Yes	12 (3.8)	9 (3.4)	0.89 (0.37–2.16)	0.89 (0.37–2.15)	5 (4.9)	1.29 (0.44–3.76)	1.25 (0.39–3.58)

SGA, small for gestational age; TTH, tension-type headache.

^a Adjusted for family history of hypertension and for occurrence of GH/PE.

However, we rarely used such drugs in our series (only five cases reported the use of triptans at least three times during pregnancy) and none of these were TTH patients. Indeed most of our cohort reported paracetamol as the first-line drug, as recommended.

Although in patients with migraine mean birth weight was lower than that in TTH patients, it was observed that TTH patients had a higher, although not statistically significant, incidence of small for gestational age infants, potentially reflecting a restriction of intrauterine foetal growth. This finding suggests that the pathogenic mechanisms of migraine and TTH on pregnancy outcome may differ. Whilst vascular mechanisms may be suggested for subjects suffering from migraine, in TTH patients a key role may be played by psychological conditions, such as anxiety or depression, which are common features amongst TTH patients. We did not investigate these aspects, however, and therefore cannot provide evidence of this association.

Since there were no differences in the mode of delivery between headache patients and controls, a potential operator-dependent effect (i.e. anxiety due to clinical conditions) on the rate of preterm delivery can be excluded. The size of the sample may well be responsible for not having found differences in pregnancy outcomes according to subtypes of migraine (with or without aura, “probable” migraine) or TTH (pure or “probable” TTH).

A secondary analysis revealed that the incidence of GH/PE was higher in headache patients than in controls. We previously reported a higher incidence of hypertensive disorders of pregnancy in patients suffering from migraine [12]. The present study, however, evinced a very high incidence of GH/PE also in TTH patients even if it did not reach statistical significance. This is a new finding that deserves further investigation. Despite the high incidence of GH/PE in the headache group, multivariate analysis revealed that both migraine and TTH are risk factors for preterm delivery independently of the occurrence of those hypertensive complications of pregnancy.

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