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Pregnancy complications and delivery outcomes in pregnant women with severe migraine

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Abstract

Objective: The objective was to study the possible association among maternal migraine during pregnancy, pregnancy complications, and the delivery outcomes: sex ratio, gestational age/birth weight and preterm birth/low birth weight.
Study design: The population-based large data set of newborn infants without any defects of the Hungarian Case–Control Surveillance System of Congenital Abnormalities, 1980–1996 was analyzed.
Results: Out of 38,151 newborn infants, 713 (1.9%) had mothers who had severe migraine during pregnancy; 68% were medically recorded. Pregnant women with severe migraine had a higher prevalence of preeclampsia and severe nausea/vomiting, but a lower occurrence of threatened abortion and preterm delivery. However, mean gestational age and birth weight, as well as the proportion of low birth weight and preterm births, were similar in newborn infants born to mothers with or without migraine.
Conclusion: Severe maternal migraine and its related drug treatment may increase the occurrence of preeclampsia and severe nausea/vomiting during pregnancy, but is not associated with unfavorable delivery outcomes.

Keywords: Migraine; Preeclampsia; Nausea and vomiting; Preterm birth; Low birth weight

1. Introduction

Migraine is a clinically heterogeneous class of craniofacial pain disorders with alteration in sensory sensitivity, autonomic dysfunction, dysregulation of mood, and neurological disturbances [1]. This clinical heterogeneity can probably be explained by the genetic complexity of migraine [2]. Migraine is among the most frequent chronic diseases, particularly in women, affecting 5–12% of the population [3]. The typical onset of migraine is between 10 and 30 years of age; it occurs therefore during pregnancy [4,5] as well. Migraine requires adequate pharmacology therapy [6–8]; thus, antimigraine drugs are frequent reasons for medical treatment in pregnant women [9].

As far as we know, no population-based epidemiological studies regarding pregnancy complications and delivery outcomes in pregnant women with migraine have been reported. Only the data of one retrospective clinical study in a migraine clinic have been published [10]. The large and population-based data set of the Hungarian Case–Control Surveillance of Congenital Abnormalities (HCCSCA) [11] is appropriate for checking the possible association between migraine during pregnancy and pregnancy complications, in addition to birth weight and gestational age, the proportion of low birth weight and preterm births in newborn infants without congenital abnormalities born to mothers with or without migraine.

2. Materials and methods

Newborn infants without congenital abnormalities were selected from the National Birth Registry of the Central

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Statistical Office for the HCCSCA. These newborn infants were controls of cases of congenital abnormality from the Hungarian Congenital Abnormality Registry [12] for the HCCSCA. In general, two controls were selected for every case, matching individually according to sex, week of birth and district of parents' residence of cases. If selected controls were twins, only one of them was randomly included in the data set of the HCCSCA. Here, pregnancy complications and delivery outcomes are evaluated only in mothers of newborn infants without congenital abnormalities, because congenital abnormalities may have a more drastic effect on these variables than migraine.

The exposure data, such as intake of medicinal products (drugs and pregnancy supplements), maternal diseases including migraine, and pregnancy complications, were obtained from three sources:

(i) Prospectively through prenatal care logbooks and other medical records.
(ii) Retrospectively by a structured questionnaire completed by mothers.
(iii) In addition, 200 non-respondent mothers were visited and questioned at home as part of a validation study [13]. The same questionnaire was used in the form of a personal interview completed by the evaluation of prenatal logbooks, discharge summaries, etc.

Here, only the 17-years data set of the HCCSCA (1980–1996) was evaluated, because the method of data collection was changed after 1996. The details of the HCCSCA's methods have been described previously [11].

Migraine disorders are broadly classified as migraine with aura or without aura [14]. Migraine without aura is a clinical syndrome characterized by headache with specific features and associated symptoms, i.e., recurrent headache disorder manifesting in attacks lasting 4–72 h with unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia. Migraine with aura is primarily characterized by the focal neurological symptoms that usually precede or sometimes accompany the headache. This recurrent disorder manifests as attacks of reversible focal neurological symptoms that usually develop gradually over 5–20 min and last for less than 60 min. However, there is a clinical overlap between these two common forms among individual migraineurs. In addition, these two forms of migraine were frequently not differentiated in the data set of the HCCSCA. These two categories of migraine were therefore analyzed together in the study.

Pregnancy complications were recorded in a prenatal logbook. Prenatal care is mandatory for pregnant women in Hungary (it is a prerequisite for getting maternity grant and leave); thus, nearly 100% of pregnant women visited prenatal care, on average 7 times during the study period. The first visit was between the 6th and 12th gestational weeks. Licensed obstetricians were obliged to record all pregnancy complications, maternal diseases, and related drug prescriptions in the logbook. Practically all deliveries occur in inpatient clinics in Hungary and birth attendants are obstetricians; thus, both birth weight and gestational age were recorded in the discharge summary of mothers. We calculated gestational age from the first day of the last menstrual period. The definition of preterm birth was less than 37 completed weeks (less than 259 days), while post-term birth was 42 completed weeks or more (i.e., 294 days or more). Thus, term births occurred in 37 to less than 42 completed weeks (259–293 days). The definition of low and high birth weight was 2499 g or less and 4500 g or more, respectively.

Information was available on 83.0% of mothers (82.6% from replies and 0.4% from visits). The time between the end of pregnancy and return of the information package including questionnaire, logbook, etc., was 5.2 ± 2.9 months. We were able to get an antenatal care logbook in 93.8% of mothers.

2.1. Statistical analysis of data

Statistical analyses were carried out with the software SAS Version 8.02 (SAS Institute, Cary, NC, USA). We calculated prevalence odds ratios (POR) and their 95% confidence intervals (CI) for categorical data, while the Student's *t*-test was used for quantitative variables. Employment status was exceptional because the Chi squared test was used for the evaluation of subgroups. At the calculation of adjusted *t* and POR, maternal age, birth order, employment status as indicator of socioeconomic status, antimigraine drugs, and pregnancy supplements were used as confounders.

3. Results

The number of births in Hungary was 2,146,574 during the study period. We sampled 38,151 of these births, representing 1.8% of Hungarian births during the study period. Out of the 38,151 newborn infants, 713 (1.9%) had mothers with migraine and it was medically recorded in the prenatal logbooks of 485 (68.0%) mothers, while the rest were based on information from the mother. Most pregnant women with migraine had medically recorded migraine treatment.

All women reported the onset of migraine before the study pregnancy with one or more migraine attacks during the study pregnancy, mainly in the third gestational month. The number of reported migraine attacks was between 1 and 19 during the study pregnancy; however, 68% of our pregnant women did not report a number of attacks, only that they suffered migraine itself. Thus, migraine was considered to be a chronic disease with ''exposure'' during the entire pregnancy.

Table 1
Maternal characteristics of pregnant women with or without migraine

Maternal variables	With migraine ($N = 713$)		Without migraine ($N = 37,438$)		Difference
	No.	%	No.	%	
Quantitative					
Maternal age (years)					
<24	298	41.8	17,696	47.3	$\chi^2_2 = 8.4$
25–29	264	37.0	12,621	33.7	$p = 0.01$
>30	151	21.2	7,121	19.0	
Mean ± S.D.	25.9 ± 5.1		25.4 ± 4.9		$t = 2.2$; $p = 0.03$
Birth order					
1	314	44.0	17,895	47.8	$\chi^2_1 = 4.0$
2 or more	399	56.0	19,543	52.2	$p = 0.04$
Mean ± S.D.	1.8 ± 0.9		1.7 ± 0.9		$t = 2.2$; $p = 0.02$
Categorical					
Unmarried	29	4.1	1,442	3.8	$\chi^2_1 = 0.1$; $p = 0.77$
Employment status					
Professional	106	14.9	4,247	11.3	$\chi^2_6 = 12.7$; $p = 0.04$
Managerial	176	24.7	9,958	26.6	
Skilled worker	215	30.2	11,475	30.7	
Semiskilled worker	96	13.5	5,687	15.2	
Unskilled worker	29	4.1	1,830	4.9	
Housewife	46	6.5	1,992	5.3	
Other	45	6.3	2,249	6.0	

Table 1 shows the demographic and social data of mothers with migraine and those without migraine for reference. Both mean maternal age and birth order were somewhat higher in mothers with migraine than in mothers without migraine due to the larger proportion of women in age groups over 25 with previous pregnancies. There was some difference in the distribution of maternal employment status due to the larger proportion of professionals and the smaller proportion of managerial and semiskilled workers among mothers with migraine.

Out of 713 mothers with migraine, 219 (30.7%) had no other diseases during the study pregnancy. In general, there was no difference in the prevalence of all but one acute maternal disorder during pregnancy between pregnant women with migraine and those without (Table 2). The exception was acute infectious diseases of the urinary tract because it occurred less frequently in pregnant women with migraine. Chronic diseases showed an unusual pattern. The commonly studied diabetes mellitus and epilepsy did not show any difference between

Table 2
The prevalence of acute and chronic maternal diseases in the group of mothers with or without migraine

Maternal diseases	With migraine ($N = 713$)		Without migraine ($N = 37,438$)		Difference POR (95% CI)
	No.	%	No.	%	
Acute diseases					
Influenza—common cold	142	19.9	6920	18.5	1.1 (0.9–1.3)
Respiratory system	66	9.3	3389	9.1	1.0 (0.8–1.3)
Digestive system	23	3.2	910	2.4	1.3 (0.9–2.0)
Urinary system	30	4.2	2271	6.1	**0.7 (0.5–0.9)**
Genital organs	46	6.5	2839	7.6	0.8 (0.6–1.1)
Others	12	1.7	500	1.3	1.2 (0.7–2.2)
Chronic diseases					
Diabetes mellitus	1	0.1	51	0.1	1.0 (0.1–7.3)
Epilepsy	3	0.4	74	0.2	2.1 (0.6–6.5)
Panic disorder	16	2.2	167	0.4	**4.7 (2.8–7.8)**
Cardiac dysrhythmias	18	2.5	99	0.3	**8.3 (5.0–13.6)**
Hemorrhoids	41	5.8	1227	3.3	**1.7 (1.3–2.4)**
Constipation	6	0.8	138	0.4	2.2 (0.9–5.0)
Thyroid disorders	7	1.0	118	0.3	**3.0 (1.4–6.4)**
Others	95	13.3	4746	12.7	1.0 (0.8–1.3)

POR: prevalence odds ratio; bold numbers show significant associations.

Table 3
The use of antimigraine drugs, the most frequently used drugs, and pregnancy supplements

Drugs	With migraine ($N = 713$)		Without migraine ($N = 37,438$)		Difference POR (95% CI)
	No.	%	No.	%	
Antimigraine drugs					
Acetylsalicylic acid	73	10.2	1431	3.8	**2.9 (2.2–3.7)**
Aminophenazone + carbromal	71	10.0	270	0.7	**15.2 (11.6–20.0)**
Aminophenazone + caffeine + phenacetin	74	10.4	53	0.1	**81.7 (56.9–117.2)**
Amitriptyline	7	1.0	0	0.0	–
Domperidone	1	0.1	0	0.0	–
Ergotamine	55	7.7	0	0.0	–
Ergotamine + aminophenazone + belladonna leaf + caffeine	22	3.1	0	0.0	–
Iprazochrome	1	0.1	0	0.0	–
Metamizole	435	61.0	1686	4.5	**33.2 (28.3–38.9)**
Metoclopramide	3	0.4	0	0.0	–
Naproxen	11	1.5	0	0.0	–
Pizotifene	10	1.4	0	0.0	–
Propranolol	35	4.9	20	0.1	**96.6 (55.5–168.2)**
Proxibarbal	6	0.8	0	0.0	–
Most frequently used drugs					
Allylestrenol	90	12.6	5267	14.1	0.9 (0.7–1.1)
Aminophylline	39	5.5	2245	6.0	0.9 (0.7–1.3)
Clotrimazole	46	6.5	3031	8.1	0.8 (0.6–1.1)
Diazepam	97	13.6	4033	10.8	**1.3 (1.1–1.6)**
Dimenhydrinate	51	7.2	1675	4.5	**1.6 (1.2–2.2)**
Drotaverine	70	9.8	3411	9.1	1.1 (0.8–1.4)
Metronidazole	13	1.8	1403	3.8	**0.5 (0.3–0.8)**
Penamecillin	55	7.7	2191	5.9	**1.3 (1.0–1.8)**
Pholedrine	38	5.3	1471	3.9	1.4 (0.9–1.9)
Promethazine	107	15.0	5918	15.8	0.9 (0.8–1.2)
Terbutaline	74	10.4	3920	10.5	1.0 (0.8–1.3)
Pregnancy supplements					
Iron	474	66.5	26,300	70.3	**0.8 (0.7–0.9)**
Calcium	68	9.5	3515	9.4	1.0 (0.8–1.3)
Folic acid	362	50.8	20,413	54.5	**0.8 (0.7–0.9)**
Vitamin B6	79	11.1	4007	10.7	1.0 (0.8–1.3)
Vitamin D	175	24.5	9975	26.6	0.9 (0.8–1.1)
Vitamin E	38	5.3	2249	6.0	0.9 (0.6–1.2)
Others or unspecified vitamins	96	13.5	4580	12.2	1.1 (0.9–1.4)
Multivitamins	35	4.9	2474	6.6	0.7 (0.5–1.0)

POR: prevalence odds ratio; bold numbers show significant associations.

pregnant women with migraine and those without. However, hemorrhoids and thyroid disorders (mainly hyperthyroidism) had a higher occurrence, while panic disorder and cardiac dysrhythmias had a much higher occurrence in mothers with migraine. Most pregnant women with cardiac dysrhythmias had paroxysmal ventricular/supraventricular tachycardia or unspecified cardiac arrhythmia.

Medicinal products were evaluated in three categories (Table 3):

(i) Nearly all antimigraine drugs were used by women with migraine during the study period. The recent antimigraine drugs such as sumatriptan and flunazarine were not used in Hungary during the study period. The so-called supplementary treatments were also more frequent in mothers with migraine.
(ii) Most frequently used other drugs, in general, showed a similar prevalence in mothers with and those without migraine. However, dimenhydrinate (an antiemetic used for nausea and vomiting in pregnancy), diazepam (the benzodiazepine drug used frequently by women with panic disorder), and penamecillin were used more frequently while metronidazole was used less frequently by mothers with migraine.
(iii) Finally, pregnancy supplements were evaluated. There was a lower use of iron and folic acid by the mothers with migraine.

The first objective of the study was to evaluate pregnancy complications of mothers with migraine (Table 4). The

Table 4
Prevalence of pregnancy complications

Pregnancy complications	With migraine ($N = 713$)		Without migraine ($N = 37,438$)		POR (95% CI)
	No.	%	No.	%	
Threatened abortion	91	12.8	6421	17.2	**0.7 (0.6–0.9)**
Nausea and vomiting, severe	100	14.0	2769	10.1	**1.5 (1.2–1.8)**
Preeclampsia[a]	81	11.4	3140	8.4	**1.4 (1.1–1.8)**
Threatened preterm delivery[b]	82	11.5	5378	14.4	**0.8 (0.6–0.9)**
Prolonged pregnancy	12	1.7	496	1.3	1.3 (0.7–2.3)
Placental disorders[c]	11	1.5	581	1.6	1.0 (0.5–1.8)
Gestational diabetes	4	0.6	266	0.7	0.8 (0.3–2.1)
Polyhydramnios	3	0.4	188	0.5	0.8 (0.3–2.6)
Oligohydramnios	0	0.0	14	0.0	–
Anemia	118	16.6	6238	16.7	1.0 (0.8–1.2)

POR: prevalence odds ratio; bold numbers show significant associations.
[a] Including pregnancy hypertension, edema, proteinuria, and extreme weight gain.
[b] Including cervical incompetence.
[c] Including placenta previa, premature separation of placenta, antepartum hemorrhage.

Table 5
Characteristics of newborn infants

Variables	With migraine ($N = 713$)		Without migraine ($N = 37,438$)		Comparison adjusted[a]	
	Mean	S.D.	Mean	S.D.	t	p
Quantitative						
Birth weight, g	3266	514	3276	511	0.6	0.53
Gestational age, weeks	39.3	2.0	39.4	2.0	0.6	0.54
	No.	%	No.	%	POR	95%CI
Categorical						
Male	485	68.0	24,314	64.9	1.1	0.9–1.3
Low birth weight	47	6.6	2120	5.7	1.2	0.9–1.6
Large birth weight	6	0.8	309	0.8	1.0	0.5–2.3
Preterm birth	70	9.8	3426	9.2	1.1	0.8–1.4
Post-term birth	63	8.8	3799	10.2	0.9	0.7–1.1

POR: prevalence odds ratio.
[a] Adjusted for maternal age and employment status and use of pregnancy supplements.

proportion of threatened abortions and threatened preterm delivery was smaller while that of severe nausea/vomiting and preeclampsia was larger in mothers with migraine than in mothers without migraine.

Table 5 summarizes the characteristics of newborn infants. Sex ratio, i.e., the proportion of males, was somewhat larger in newborn infants born to mothers with migraine compared with the group of mothers without migraine. Mean gestational age was 0.1 weeks shorter in the mothers with migraine compared with mothers without migraine. The difference was 10 g in the mean birth weight between live babies born to mothers with and without migraine. Both the proportion of preterm births and low birth weight was slightly, but not significantly larger in the group of mothers with migraine. The rate of post-term births was somewhat lower in pregnant women with migraine while the proportion of large birth weight babies was similar in the two study groups. There was no difference in these variables between male and female newborn infants born to mothers with or without migraine.

4. Discussion

Our study showed a higher prevalence of severe nausea/vomiting and preeclampsia, but a lower occurrence of threatened abortion and preterm delivery in pregnant women with migraine. However, there was no difference in mean gestational age and birth weight in newborn infants born to women with or without migraine, as well as the proportion of low birth weight and preterm birth.

The strengths of HCCSCA can be explained by the large and population-based data set of an ethnically homogeneous European (Caucasian) population in which 68% of migraines were recorded by medical professionals before the birth (i.e., prospectively); in addition, pregnancy complications, gestational age, and birth weight were

medically recorded and potential confounding factors were available for analysis. Of course, the limitations of the data set need to be mentioned as well:

(i) The diagnosis of migraine was based on the reported data; thus, the diagnostic criteria of migraine and the differentiation between migraine and other headaches could not be checked.
(ii) There was a lower prevalence of migraine during pregnancy in our study (about 2%) than expected (5–10%) on the basis of previous studies [1,3]. However, in general the frequency of migraine attacks decreases during pregnancy [4,5] and it is likely that only the more severe migraines for which antimigraine treatments were used were recorded in the logbooks. Thus, the under-ascertainment of migraine during the study pregnancy can be considered; in addition, our pregnant women might only have the severe form of migraine.
(iii) Response rate was 83% and only 200 non-respondent mothers were visited at home, because the Ethics Committee considered that this follow-up would be disturbing to the parents of healthy children. The prevalence of maternal diseases including migraine, however, did not show differences between respondent and nonrespondent families [13].
(iv) Another major weakness of our study is the lack of maternal smoking and drinking of alcohol as confounders in the total data set. Our previous validation study showed the low reliability of retrospective maternal self-reported information regarding smoking and drinking during the study pregnancy [15]; therefore, these data were collected only in the subset of our study based on the home visit. Out of 3022 mothers visited at home by regional nurses, 18% of the total data set were smokers. Out of the 200 mothers in another study [13], 38 (19%) smoked during pregnancy, and this corresponded to the figure for the whole Hungarian population. Excessive drinking of alcohol was not recorded.

In the migraine clinic of Wainscott et al. [10], out of 777 women with migraine, 450 (57.9%) had been pregnant, while out of 182 women without migraine, 136 (74.7%) had been pregnant. The prevalence of fetal death (miscarriages and stillbirths) was similar in the study groups (27% versus 29%). The occurrence of toxemia was same (18%) for both study groups. There were 924 and 277 live births to mothers with or without migraine and the rates of congenital abnormalities were 2.16 and 2.52%, respectively.

The higher proportion of preeclampsia in pregnant women with migraine in our study is worth mentioning because maternal migraine has not been mentioned among the risk factors for preeclampsia [16]. The possible association between maternal migraine and a higher rate of preeclampsia can be explained by the vascular origin of these two pathological conditions [17]. In addition, several epidemiological studies have suggested that the frequency of preeclampsia is inversely proportional to nutritional calcium intake [18]. A migraine-specific gene at chromosome 19p13 is known to be associated with missense mutations in the brain-expressed voltage-gated alfa1Aca^{2+}-channel subunit gene: CACNA1A [19]. Recently, a model of the potential integration of migraine susceptibility factors into CACNA1A-dependent pathways was presented [2]. The occurrence of severe nausea and vomiting during pregnancy was also higher in women with migraine; the latter may associate with a lower rate of early fetal death [20,21] and this finding was in agreement with the lower occurrence of threatened abortion and preterm delivery in our study.

A somewhat higher proportion of males born to mothers with migraine was found in the study. The sex ratio (male/male + female) was 51% in the Hungarian newborn population during the study pregnancy. However, cases of congenital abnormalities have a male predominance (65%) due to mainly the higher occurrence of defects in male genital organs (undescended testis and hypospadias) and controls were matched to the sex of cases. It explains the high proportion of males among the newborn infants born to mothers without migraine (about 65%). However, the proportion of males born to mothers with migraine was larger—near to the level of significance ($p = 0.09$). There are three possible explanations for this association:

(i) Male fetuses induce a somewhat higher risk of migraine attack during pregnancy;
(ii) male fetuses have a lower rate of prenatal selection (i.e., fetal death) in the offspring of pregnant women with migraine, in agreement with the lower proportion of threatened abortion and preterm delivery; and last but not least
(iii) chance effect.

It is strange that the possible effects of drugs during pregnancy have been evaluated frequently, but the possible hazard of underlying maternal diseases, e.g., migraine, has rarely been studied. On the other hand, it is interesting to study further the possible association between migraine and hyperthyroidism, panic disorder, and cardiac dysrhythmias, which were more frequent in pregnant women with migraine.

In conclusion, our findings indicate that severe migraine in pregnant women treated with antimigraine drugs is associated with a higher prevalence of preeclampsia and severe nausea/vomiting, but a lower occurrence of threatened abortion and preterm delivery. However, the major finding is that maternal migraine does not constitute a hazard for delivery outcomes, i.e., it does not increase the likelihood of preterm birth and low birth weight.

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References

[1] Mathew NT. Pathophysiology, epidemiology and impact of migraine. Clin Cornerstone 2001;4:1–17.

[2] Esterez M, Gardner KL. Update on the genetics of migraine. Hum Genet 2004;114:225–35.

[3] MacGregor EA, Brandes J, Eikermann A. Migraine prevalence and treatment: the Global Migraine and Zomitriptan Evaluation Survey. Headache 2003;43:19–26.

[4] Massey EW. Migraine during pregnancy. Obstet Gynecol Surv 1977;32:693–6.

[5] Reik Jr L. Headaches in pregnancy. Semin Neurol 1988;8:187–92.

[6] Diamond S. Migraine headache prevention and management. New York: Marcel Dekker; 1990.

[7] Silberstein SD, Lipton RB. Headache in clinical practice Oxford: Medical Media; 1998.

[8] Lance JW. The pharmacotherapy of migraine. Med J Aust 1986;44:85–8.

[9] Czeizel AE, Rácz J. Evaluation of drug intake during pregnancy in the Hungarian Case–Control Surveillance of Congenital Anomalies. Teratology 1990;42:505–12.

[10] Wainscott G, Sullivan FM, Volans GN, Wilkinson M. The outcome of pregnancy in women suffering from migraine. Postgrad Med J 1978;54:98–102.

[11] Czeizel AE, Rockenbauer J, Siffel CS, Varga E. Description and mission evaluation of the Hungarian Case–Control Surveillance of Congenital Abnormalities, 1980–1996. Teratology 2001;63:176–85.

[12] Czeizel AE. First 25 years of the Hungarian Congenital Abnormality Registry. Teratology 1997;55:299–305.

[13] Czeizel AE, Petik D, Vargha P. Validation studies of drug exposures in pregnant women. Pharmacoepidemiol Drug Saf 2003;12: 409–16.

[14] Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders. 2nd ed. Cephalgia 2004; 24: Suppl. 1. p. 1–151.

[15] Czeizel AE, Petik D, Vargha P. Smoking and alcohol drinking during pregnancy. The reliability of retrospective maternal self-reported information. Cent Eur J Public Health 2004;12:179–83.

[16] Dekker G, Sibai B. Primary, secondary and tertiary prevention of preeclampsia. Lancet 2001;357:209–15.

[17] Villalon CM, Centurion D, Valdivia LF, et al. Migraine: pathophysiology, pharmacology, treatment and future trends. Curr Vasc Pharmacol 2003;1:71–84.

[18] Marcoux S, Brisson J, Fabia J. Calcium intake from dairy products and supplements and the risks of preeclampsia and gestational hypertension. Am J Epidemiol 1991;133:1266–72.

[19] Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the CA^{2+} channel gene CACNL1A4. Cell 1996;87:543–52.

[20] Medalie JH. Relationship between nausea and/or vomiting in early pregnancy and abortion. Lancet 1957;273:117–9.

[21] Weigel MM, Weigel R. Nausea and vomiting of early pregnancy and pregnancy outcomes. An epidemiological study. Br J Obstet Gynecol 1989;96:1304–11.