ORIGINAL RESEARCH ARTICLE

Drug Saf 2011; 34 (8): 691-703
0114-5916/11/0008-0691/$49.95/0

Delivery Outcome after Maternal Use of Drugs for Migraine

A Register Study in Sweden

Bengt Källén,[1] *Emma Nilsson*[2] and *Petra Otterblad Olausson*[2]

1 Tornblad Institute, University of Lund, Lund, Sweden
2 Department of Statistics, Monitoring and Analyses, National Board of Health and Welfare, Stockholm, Sweden

Abstract

Background: The use of drugs for migraine during pregnancy may have adverse effects on delivery outcome, and warnings exist for such drugs regarding use during pregnancy. Most information in the literature concerns triptans.
Objective: The aim of the study was to describe the delivery outcome when a woman had used drugs for migraine during pregnancy.
Study Design: A register study where exposure for drugs was obtained partly by interview conducted by the attending antenatal care midwife and medical records from antenatal care (1995–2008) and partly by linkage to the Prescribed Drug Register (2005–8).
Setting: All deliveries in Sweden (1 211 670 women) recorded in the Medical Birth Register with data from antenatal care.
Patients: Women using triptans or ergots during pregnancy were identified and compared with all women who did not use drugs for migraine.
Main Outcome Measures: Pregnancy complications, pregnancy duration and birthweight, neonatal morbidity and mortality, and congenital malformations.
Results: Use of ergots or triptans during early pregnancy (first trimester) occurred in 3286 women with 3327 infants, while use after the first trimester occurred in 1394 women with 1419 infants. Women using such drugs for migraine were older than other women, were more often of parity 1 (no previous infant) and more often had a high body mass index. Women using drugs for migraine had not previously had more miscarriages than expected. There was an increased risk for pre-eclampsia (odds ratio [OR] 1.44; 95% CI 1.17, 1.76). An increased risk for preterm birth was seen after use of drugs for migraine later in pregnancy (OR 1.50; 95% CI 1.22, 1.84). There was no increased risk for stillbirth or early neonatal death. No certain signs of teratogenicity were found for any of the drug types when compared with women not using such drugs (OR for any malformation 0.95; 95% CI 0.80, 1.12).

Conclusions: Our data suggest that the risk of adverse effects on pregnancy outcome associated with the use of drugs for migraine is low but data for triptans other than sumatriptan are still few.

Background

Most recent studies on the possible adverse effects of drugs used to treat migraine during pregnancy concern triptans, notably sumatriptan. In 1998, a review warned against the use of triptans during pregnancy;[1] however, a more recent review of available data,[2] later updated,[3] found no evidence of a teratogenic effect of sumatriptan; this has been verified by later studies. Cunnington et al.[4] summarized data from the Sumatriptan and Naratriptan Pregnancy Registry (479 first-trimester exposed women), kept by GlaxoSmith-Kline, and Nezvalová-Henriksen et al.[5] reported data from the prospective Norwegian Mother and Child Cohort Study (1535 exposed women). The former study contained 50 women who had used naratriptan,[4] while the latter study comprised cases of first-trimester exposure to sumatriptan (653), rizatriptan (328), zolmitriptan (243), eletriptan (179), naratriptan (31) and almotriptan (29).[5] These authors found a slightly increased risk for atonic uterus and haemorrhage after triptan use during pregnancy but no teratogenic effect.

Less information is available about the use of ergots during pregnancy. Heinonen et al.[6] described 25 mother-child pairs after ergotamine exposure and 32 after exposure to other ergots; two and three infants were malformed, respectively. Källén and Lygner[7] described pregnancy outcome in 53 pregnancies with maternal use of dihydroergotamine, and 213 with use of ergotamine combinations, without finding any evidence for teratogenicity.

In a letter to the editor, Bánhidy et al.[8] claimed that high doses of ergotamine could have a teratogenic effect, which was not seen at low doses. This study was based on the Hungarian case-control study with data from 1980 to 1986 and found 13 exposed infants among 9460 cases and 17 among 16 160 controls, giving an odds ratio (OR) of 1.3 (95% CI 0.6, 2.7), thus not statistically significant. When separating the cases into specific groups, numbers became very low and all statistical estimates uncertain. There were three cases of neural tube defects after maternal use of ergotamine 1.5 mg daily but none after 0.3 mg, which led the authors to suggest that a high dose of ergotamine may be teratogenic.

An association between migraine attacks during early pregnancy and congenital limb defects was suggested by the same authors.[9] In a separate study,[10] the authors found no effect of migraine on pregnancy duration and birthweight but found an increased risk for severe nausea and vomiting during pregnancy, and pre-eclampsia.

A later study[11] claimed that maternal use of ergotamine was associated with a slight reduction in pregnancy duration (0.7 weeks) and birthweight (196 g) when 77 pregnancies with ergotamine exposures were compared with over 38 000 pregnancies without such exposures. In all, this study contained nine exposed preterm infants – seven males and two females.

A number of case reports have been published associating the use of ergots during pregnancy with malformations of so-called vascular origin, e.g. jejunal atresia,[12] polymicrogyria[13] and Möbius sequence.[14]

The present study was conducted in order to update analyses on the use of drugs used to treat migraine during pregnancy from the Swedish National Health Register system, notably pregnancy complications, pregnancy duration and birthweight, neonatal morbidity and mortality, and congenital malformations. Some of the data have previously been published: data for 1995–9[4], sumatriptan data for a comparison with the Sumatriptan and Naratriptan Pregnancy Registry[7] and as part of an overview of drug use during pregnancy.[15]

Methods

Data were obtained from the Swedish Medical Birth Register.[16] Information in the register is based on copies of the medical documents from the antenatal care, delivery and paediatric examination of the newborn.

Pregnant women who attend antenatal clinics in Sweden (which the vast majority do) are interviewed by a midwife and asked about drugs used since the pregnancy started. This interview is usually made before the end of the first trimester (usually between weeks 10 and 12 of pregnancy). Since 1 July 1994, information on the drug name has been stored in the Medical Birth Register as clear text but later transferred into Anatomical Therapeutic Chemical codes with a semi-automatic process.[17] Information on dosage and timing is often incomplete. The Medical Birth Register also contains information on drugs prescribed during antenatal care. This information was supplemented with data from the Swedish Prescribed Drug Register,[18] which contains information on all prescription drugs bought in the country since 1 July 2005. Specific drug use during pregnancy was identified from the day of redeeming the prescription compared with the date of delivery and the estimated pregnancy duration in days.

Data were obtained from the Medical Birth Register for the period 1 July 1995 to the end of 2008, supplemented with data from the Prescribed Drug Register for the period 1 July 2006 to the end of 2008. The material was divided into two parts: early use (comprising the first trimester, herein described as first-trimester use) with information solely from the Medical Birth Register, and later use (after the first trimester based on information from the Medical Birth Register and the Prescribed Drug Register, herein described as second- and/or third-trimester use). The latter material will be incomplete because no information from this register was used before 1 July 2006. The two data sources were combined for the purpose of this study.

From the antenatal care form, completed by the attending midwife and based on the interview at the first antenatal visit, information was obtained on maternal age (five year groups, <20, 20–24, etc.), maternal smoking in early pregnancy (unknown, none, <10 cigarettes per day, ≥10 cigarettes per day), number of previous miscarriages (0, 1, 2, ≥3), number of years of unwanted childlessness as an estimate of subfertility (0, 1, 2, 3, 4, ≥5), pre-pregnancy weight and height from which body mass index (BMI) was estimated (unknown, <19.8, 19.8–25.9, 26–29.9, 30–39.9, ≥40), maternal cohabitation (unknown, cohabiting, living alone, other) and work outside home (unknown, full-time, part-time, none). By linkage with the birth register of Statistics Sweden, parity (1 to ≥4, where 1 means first infant born) and maternal country of birth were added. By linkage with the Register of Education, maternal education level in 2002 was obtained for women who gave birth in 1995–2001.

From the delivery unit form, information was obtained on maternal pregnancy diagnoses based on International Classification of Diseases (ICD) codes and information on delivery induction if the delivery did not start with a caesarean section, and caesarean section.

From the paediatric form, completed by the attending paediatrician, information was obtained on pregnancy duration (mainly estimated from second-trimester sonography), number of infants in the birth, infant sex, birthweight, 5-minute Apgar score (low Apgar score is <7), stillbirth, early neonatal death among live births, neonatal diagnoses based on ICD codes, use of continuous positive airway pressure (CPAP), or mechanical ventilation. The presence of congenital malformations was ascertained from multiple sources: the paediatric form of the Medical Birth Register, the Register of Birth Defects (previously Register of Congenital Malformations) and the Patient Register (previously Hospital Discharge Register).[19] Intrauterine growth was evaluated from sex- and parity-specific birthweight per pregnancy-week graphs based on data in the Medical Birth Register.[20] Small for gestational age (SGA) was <2 standard deviations (SDs) below expected birthweight, while large for gestational age (LGA) was >2 SDs above expected birthweight.

All linkage between registers was performed using the 12-digit personal identification number that everyone living in Sweden has.

Women who had used drugs for migraine in early pregnancy were compared with all other

women giving birth when records from the first antenatal visit were available. The total studied cohort comprised 1 211 670 women.

Statistics

Most analyses (when the expected number was ten or more) were made using Mantel-Haenszel OR estimates, adjusting for confounders of interest: year of delivery, maternal age, parity, maternal smoking and BMI. Miettinen's method was then used to estimate 95% confidence intervals (CIs). When the expected number of cases was below ten, risk ratios were calculated as observed number divided by expected number, the latter calculated after adjustment for year of delivery, maternal age, parity, maternal smoking and BMI. The CI was then based on exact Poisson estimates. Two ORs were compared with z-tests, based on the Mantel-Haenszel variances.

Ethics

The study was performed within the responsibilities of the National Board of Health and Welfare, therefore no ethical approval from outside ethical committees was needed.

Results

Summary of the Use of Drugs for Migraine

First-trimester exposure of drugs for migraine was identified for 3327 infants born to 3286 women, and second- and/or third-trimester exposure was identified for 1419 infants born to 1394 women. Among infants exposed after the first antenatal visit (after the first trimester), 488 were identified only in the Medical Birth Register, 793 only in the Prescribed Drug Register and 138 in both registers. For the period 1 July 2006 to the end of 2008, 232 infants were identified from the Medical Birth Register, and 138 (40%) of these were also found in the Prescribed Drug Register. Explanation as to the discrepancy between the registers is that in the Medical Birth Register regarding drug use after the first trimester, information is provided on what drugs the woman was prescribed or advised to use; in some 60% of cases the prescription was not redeemed or drugs purchased previously were used.

When the specific drugs identified from the Prescribed Drug Register were compared with those identified in the Medical Birth Register, in

Table I. Number of women using specific drugs for migraine in early pregnancy and later in pregnancy

ATC code	Drug name	Number of women	
		first-trimester use	second- and/or third-trimester use
N02CA01	Dihydroergotamine	135	105
N02CA04	Methysergide	1	0
N02CA07	Lisuride	1	0
N02CA52/72	Ergotamine combination	381	12
N02CA	Unspecified ergot	2	0
N02CA	Any ergot	519	115
N02CC01	Sumatriptan	2229	937
N02CC02	Naratriptan	22	9
N02CC03	Zolmitriptan	357	166
N02CC04	Rizatriptan	155	122
N02CC05	Almotriptan	6	21
N02CC06	Eletriptan	13	9
N02CC	Any triptan	2742	1215
N02CX01	Pizotifen	64	79
N02C	Unspecified drug for migraine	10	0

Table II. Characteristics of women reporting the use of drugs for migraine in early pregnancy

Variable	Number using drugs for migraine	Total number of women	OR[a] (95% CI)
Maternal age (y)[b]			
<20	27	22 459	0.41 (0.28, 0.60)
20–24	272	169 181	0.53 (0.47, 0.60)
25–29	937	393 445	0.82 (0.76, 0.89)
30–34	1201	412 556	1.14 (1.07, 1.23)
35–39	706	182 430	1.60 (1.46, 1.74)
40–44	138	33 547	1.56 (1.31, 1.86)
≥45	5	1 338	1.44 (0.60, 3.45)
Parity[b]			
1	1574	532 568	1.44 (1.34, 1.55)
2	988	439 256	0.73 (0.68, 0.79)
3	516	168 081	1.01 (0.92, 1.12)
≥4	208	75 051	0.82 (0.70, 0.95)
Smoking			
Unknown	59	31 546	Not analysed
None	2902	1 055 690	1.00 (reference)
<10 cigarettes/day	224	89 053	1.01 (0.88, 1.16)
≥10 cigarettes/day	101	38 667	0.99 (0.81, 1.22)
Previous miscarriages			
None	2647	968 150	1.00 (reference)
1	447	189 080	0.87 (0.79, 0.97)
2	110	41 676	0.88 (0.72, 1.07)
≥3	52	16 050	1.06 (0.80, 1.40)
Body mass index			
Unknown	309	123 120	Not analysed
<19.8	257	95 759	1.10 (0.96, 1.24)
19.8–25.9	1849	699 131	1.00 (reference)
≥26	871	296 446	1.12 (1.03, 1.21)
Total number of women	3286	1 214 956	

a ORs were adjusted for year of delivery and all other variables.

b Each group is compared with all other age and parity groups.

OR = odds ratio.

most cases the drugs stated in the two registers were identical; however, in ten cases discrepancies were found. In six of these cases, a prescription had been filled that was not reported in the Medical Birth Register and in three of these cases, a drug was reported but no prescription was identified. In the remaining case, the prescription was for sumatriptan and the drug stated in the Medical Birth Register was dihydroergotamine.

The number of women who had used individual drugs for migraine is shown in table I, irrespective of the use of other drugs for migraine. Most exposures thus involved sumatriptan, and the total number of first-trimester ergot exposure was only 519. Use after the first trimester, which was identified from either the Medical Birth Register or the Prescribed Drug Register, is consistently lower than first-trimester use, with the exception of almotriptan and pizotifen. The low usage of ergotamine in later pregnancy is especially notable.

Twenty-four women reported the use of two drugs for migraine in early pregnancy, in ten of whom the combination was sumatriptan and zolmitriptan. During the second and/or third trimesters,

53 women had received prescriptions for two different drugs, in 23 of whom the prescription was for sumatriptan and zolmitriptan.

Use of drugs for migraine in both the first trimester and later in pregnancy occurred in 341 women. If the comparison was restricted to the period 1 July 2006 to the end of 2008 (when data from the Prescribed Drug Register were available), 179 among 528 first-trimester users also used such drugs in the second and/or third trimester (34%), while among 1008 women who used these drug after the first trimester, 18% had reported such drugs also in the first trimester.

Characteristics of Women Reporting use of Drugs for Migraine in Early Pregnancy

Tables II and III compare women reporting the use of drugs for migraine in early pregnancy with all women who gave birth in Sweden during the period 1 July 1995 to the end of 2008. Increased maternal age and parity 1 were associated

Table III. Other maternal characteristics of women reporting the use of drugs for migraine in early pregnancy

Variable	Number using drugs for migraine	Total number of women	OR[a] (95% CI)
Years of unwanted childlessness			
0	2977	1 123 707	1.00 (reference)
1	87	26 761	1.12 (0.90, 1.39
2	97	26 603	1.17 (0.95, 1.43)
3	45	14 482	0.94 (0.70, 1.27)
4	30	8 184	1.07 (0.75, 1.54)
≥5	50	15 223	0.91 (0.67, 1.21)
Country of birth			
Unknown	7	10 949	Not analysed
Sweden	2954	982 272	1.00 (reference)
Other Nordic country	66	27 127	0.77 (0.60, 0.98)
Non-Nordic country	259	194 608	0.47 (0.41, 0.53)
Family situation			
Unknown	54	24 969	Not analysed
Co-habiting	3070	1 126 493	1.00 (reference)
Living alone	74	30 296	0.94 (0.75, 1.19)
Other	88	33 197	1.07 (0.87, 1.33)
Work outside home			
Unknown	348	158 879	Not analysed
Full-time	1687	561 685	1.00 (reference)
Part-time	804	281 514	1.07 (0.97, 1.16)
None	442	212 878	0.85 (0.76, 0.95)
Maternal education (y)[b]			
Unknown	20	17 516	Not analysed
<9	16	10 227	0.60 (0.36, 1.01)
9–11	124	54 352	0.98 (0.80, 1.20)
12	791	285 514	1.00 (reference)
13	96	29 953	1.05 (0.84, 1.30)
14	440	152 624	0.86 (0.76, 0.97)
>14	5	2 889	0.49 (0.21, 1.16)

a OR adjusted for year of birth, maternal age, parity and smoking.

b Data only available for 1996–2001; 1410 women with drugs for migraine, 506 328 in population.

OR = odds ratio.

Table IV. Concomitant drug use by women reporting drugs for migraine in early pregnancy

Concomitant drug group	Number using drugs for migraine	Total number of women	OR/RR[a] (95% CI)
Drugs for stomach ulcer and reflux	90	9 973	3.23 (2.64, 3.95)
Folic acid	105	54 730	0.66 (0.55, 0.80
Drugs for hypertension	121	4 534	8.98 (7.70, 10.5)
β-blockers	114	3 921	9.73 (8.32, 11.4)
Oral contraceptives	18	3 599	2.01 (1.20, 3.18)[b]
Gestagens	11	4 924	0.66 (0.37, 1.19)
Systemic corticosteroids	18	4 138	1.55 (0.97, 2.46)
Thyroid drugs	53	15 791	1.13 (0.86, 1.49)
Antibiotics	98	35 464	1.04 (0.85, 1.27)
NSAIDs	265	18 843	5.13 (4.58, 5.75)
Opioids	165	5 947	10.4 (9.07, 11.08)
Minor analgesics	728	85 817	3.66 (3.39, 3.96)
Anticonvulsants	13	3 272	1.44 (0.77, 2.46)[b]
Antipsychotics	11	3 653	1.06 (0.59, 1.91)
Sedatives/hypnotics	64	5 324	4.14 (3.29, 5.22)
Antidepressants	135	15 244	3.27 (2.76, 3.86)
Drugs for rhinitis	72	15 584	1.60 (1.27, 2.02)
Antiasthmatics	177	35 781	1.85 (1.59, 2.15)
Antihistamines	220	66 859	1.24 (1.08, 1.43)
Antihistamines for nausea and vomiting in pregnancy	151	51 738	1.11 (0.94, 1.31)
Antihistamines for allergy	76	17 214	1.58 (1.20, 1.98)

a OR adjusted for year of birth, maternal age, parity and smoking. Women reporting drugs for migraine (n = 3286) compared with women in population (n = 1 268 563).

b RR as observed over expected numbers.

OR = odds ratio; **RR** = relative risk.

with increased use of drugs for migraine; use was especially low in women at parity 2. No association was found with smoking but an increased use was observed at high BMI, and no clear-cut effect was seen in subfertility. Lower use was found among women born outside Sweden, no definite difference was seen between cohabiting women and other women, and lower use was observed in women not working outside the home. Previous miscarriages were not more common among exposed women; this was also true if the analysis was restricted to women using ergots (OR 0.82; 95% CI 0.65, 1.03).

Concomitant drug use is shown in table IV. The strong associations between drugs for migraine and analgesics (opioids, minor analgesics, NSAIDs) and β-blockers are easy to understand. There are also significant associations (although weaker) with drugs for stomach ulcer, sedatives/hypnotics and antidepressants, drugs for rhinitis or asthma, and antihistamines for allergy. Finally, there is an association with the use of oral contraceptives into pregnancy.

Pregnancy Complications among Women Using Drugs for Migraine

The results of comparisons between women who used drugs for migraine and women who did not are shown in table V. The only diagnosis that occurs at a significantly increased rate in both first trimester and later exposed pregnancies is pre-eclampsia The risk for chronic hypertension is increased but is significant only following

Table V. Maternal delivery diagnoses in women who used drugs for migraine during pregnancy compared with those in women who did not use drugs for migraine during pregnancy

Diagnosis	Total number of women	First-trimester exposure		Second- and/or third-trimester exposure	
		number using drugs for migraine	OR[a] (95% CI)	number using drugs for migraine	OR[a] (95% CI)
Pre-existing diabetes mellitus	16 862	31	0.64 (0.45,0.91)	34	1.26 (0.89, 1.80)
Gestational diabetes	11 852	34	1.00 (0.71,1.41)	21	1.09 (0.70, 1.71)
Chronic hypertension	14 850	54	1.23 (0.94,1.61)	38	1.50 (1.08, 2.09)
Pre-eclampsia	57 913	226	1.40 (1.22,1.61)	105	1.44 (1.17, 1.76)
Hyperemesis gravidarum	12 494	37	1.02 (0.73,1.41)	24	1.14 (0.75, 1.73)
Placenta previa	14 269	37	0.88 (0.63,1.22)	25	1.05 (0.70, 1.57)
Placental abruption	15 345	46	1.03 (0.77,1.38)	28	1.14 (0.77, 1.67)
PROM	30 569	76	0.87 (0.70,1.11)	46	1.09 (0.81, 1.47)
Antepartum bleeding	17 975	47	0.93 (0.70,1.25)	30	1.15 (0.79, 1.67)
Intrapartum bleeding	26 515	84	1.09 (0.87,1.36)	51	1.19 (0.90, 1.58)
Postpartum bleeding	76 163	208	1.04 (0.91,1.20)	84	0.95 (0.76, 1.18)
Delivery induction	140 255	455	1.25 (1.13,1.38)	235	1.42 (1.23, 1.65)
Caesarean section	205 139	623	1.09 (1.00,1.19)	337	1.32 (1.16, 1.50)

a OR adjusted for year of birth, maternal age, parity, smoking and body mass index.

OR = odds ratio; **PROM** = premature rupture of membranes.

exposure after the first trimester. Both delivery inductions and caesarean sections occur at increased rates in exposed pregnancies.

When pregnancy complications were analysed after exposure to ergots, the OR estimate for pre-eclampsia after first-trimester exposure (based on 36 cases) was 1.48 (95% CI 1.06, 2.08); after later exposure there were only five cases, therefore no OR was calculated. There was no increase in risk of delivery inductions: OR after first-trimester ergot exposure was 0.92 (95% CI 0.69, 1.23) and 1.01 (95% CI 0.54, 1.87) after later exposure, based on 52 and 12 cases, respectively. The risk for caesarean section (based on 100 cases) was 1.20 (95% CI 0.96, 1.50) after first-trimester ergot exposure and 1.37 (95% CI 0.86, 2.21) after later exposure (based on 22 cases).

When the analyses of pre-eclampsia, delivery induction and caesarean section were repeated for first-trimester exposures excluding women who also reported the use of β-blockers,

Table VI. Pregnancy duration and birthweight in singleton infants after maternal use of drugs for migraine

Outcome	Total number of women	First-trimester exposure		Second- and/or third-trimester exposure	
		number using drugs for migraine	OR[a] (95% CI)	number using drugs for migraine	OR[a] (95% CI)
<37 wk[b]	58 195	167	1.01 (0.86, 1.18)	102	1.50 (1.22, 1.84)
<2500 g[c]	37 323	101	0.95 (0.78, 1.16)	101	1.19 (0.90, 1.58)
≥4500 g[c]	47 929	140	1.07 (0.90, 1.26)	34	0.62 (0.44, 0.87)
SGA[d]	25 839	71	0.95 (0.75, 1.20)	36	1.20 (0.86, 1.68)
LGA[d]	71 190	203	1.07 (0.93, 1.24)	75	0.89 (0.70, 1.13)

a OR adjusted for year of birth, maternal age, parity, smoking and body mass index.

b Total number of singletons with known gestational duration = 1 196 394, after early drug exposure = 3245 and after later drug exposure = 1368.

c Total number of singletons with known birthweight = 1 192 677, after early drug exposure = 3235 and after later drug exposure = 1362.

d Total number of singletons with known gestational duration, birthweight and sex = 1 192 133, after early drug exposure = 3234 and after later drug exposure = 1362.

LGA = large for gestational age; **OR** = odds ratio; **SGA** = small for gestational age.

Table VII. Neonatal diagnoses among infants whose mothers had used drugs for migraine in early or later pregnancy

Diagnosis	Total number of women	First-trimester exposure		Second- and/or third-trimester exposure	
		number using drugs for migraine	OR[a] (95% CI)	number using drugs for migraine	OR[a] (95% CI)
All infants	1 233 228	3327	Reference	1419	Reference
Hypoglycaemia	43 239	128	0.98 (0.82, 1.17)	52	0.97 (0.74, 1.30)
Respiratory diagnoses	48 752	121	0.86 (0.72, 1.03)	65	1.07 (0.83, 1.38)
CPAP	15 645	39	0.81 (0.59, 1.12)	17	0.99 (0.61, 1.61)
Mechanical ventilation	11 120	35	1.04 (0.74, 1.45)	17	1.25 (0.77, 2.03)
Low Apgar score	23 801	65	0.92 (0.72, 1.18)	35	1.14 (0.81, 1.60)
Intracranial haemorrhage	11 403	37	1.08 (0.78, 1.50)	17	1.18 (0.73, 1.91)
Neonatal convulsions	10 388	34	1.08 (0.77, 1.52)	16	1.23 (0.74, 2.01)
Jaundice	58 712	178	1.07 (0.92, 1.24)	86	1.17 (0.94, 1.46)

a OR adjusted for year of birth, maternal age, parity, smoking and body mass index.

CPAP = continuous positive airway pressure; **OR** = odds ratio.

NSAIDs, opioids, sedatives or hypnotics, antidepressants or antiasthmatic drugs (all drugs that were used in excess with drugs for migraine and that may affect outcome), the ORs decreased but remained statistically significant for pre-eclampsia (OR 1.29; 95% CI 1.09, 1.52) and delivery induction (OR 1.15; 95% CI 1.02, 1.29) but the effect on caesarean section disappeared (OR 1.01; 95% CI 0.91, 1.12).

Infant Outcome after Maternal Use of Drugs for Migraine

Sex

After first-trimester use, there were 1714 boys and 1612 girls (one infant with unknown sex), a sex ratio of 1.06 (95% CI 0.99, 1.14), and after second- and/or third-trimester use there were 727 boys and 692 girls, a sex ratio of 1.05 (95% CI 0.95, 1.17). Both estimates are thus close to the normal sex ratio of 1.06.

Multiple Births

After early exposure, the twinning rate was non-significantly low (OR 0.74; 95% CI 0.54, 1.01), and after later exposure the rate was non-significantly high (OR 1.19; 95% CI 0.80, 1.17).

Pregnancy Duration and Birthweight in Singleton Infants

Table VI shows the results of analyses of gestational duration and birthweight. The only significantly increased OR is for preterm births after second- and/or third-trimester exposure. For use of ergots during the second and/or third trimester, the relative risk (RR) is 2.56 (95% CI 1.40, 4.29) based on 14 cases, and for triptans the RR is 1.31 (95% CI 1.03, 1.67) based on 72 cases. The difference may be random.

Neonatal Diagnoses

Table VII shows ORs for a number of selected neonatal diagnoses after maternal use of drugs for migraine. None of the ORs reaches statistical significance. Only a few infants exposed to ergots during the first trimester had any of the following diagnoses: hypoglycaemia, treatment with CPAP, treatment with mechanical ventilation, neonatal convulsions, intracerebral haemorrhage (one case for each diagnosis), respiratory problems (n = 4), low Apgar score (n = 3) and jaundice (n = 7) [RR 1.38; 95% CI 0.56, 2.86].

There was no increased risk for stillbirths after first-trimester (ten observed; RR 0.82; 95% CI 0.39, 1.51) or second- and/or third-trimester (three observed; RR 0.51; 95% CI 0.11, 1.50) exposure. Nine of the former group and all three among the latter group were exposed to triptans. There was no increased risk for death before 7 days of age. After early exposure, seven infants died (RR 1.03; 95% CI 0.41, 2.12) and after later exposure two died (RR 0.86; 95% CI 0.10, 3.12).

Congenital Malformations

Table VIII provides an overview of different congenital malformations identified in infants of mothers using drugs for migraine (any type) in early pregnancy. The concept 'relatively severe malformations' includes all malformations with the exception of infants who have only one or more of the following diagnoses: preauricular appendix, tongue tie, patent ductus arteriosus at preterm birth, single umbilical artery, undescended testicle, unstable hip and nevus. These are common and clinically less significant conditions that show a marked registration variation between hospitals. These exclusions reduce the malformation rate in the population from 4.6% to 3.2%.

Most ORs for specific malformations are based on low numbers and have large CIs. Oesophageal atresia shows the highest OR but it is not statistically significant and is based on three cases. All three were exposed to sumatriptan.

Division of the data according to the group of drugs for migraine or specific drugs is given in tables IX and X. Data on ergots are limited but indicate no significant teratogenicity. For specific drugs, with the exception of sumatriptan, most CIs are wide. The only high OR that reaches formal statistical significance is for eleptriptan, but the risk estimate is based on only three malformed infants among 14 exposed. The malformation diagnoses among the three infants differ;

Table VIII. Congenital malformations in infants born to women who reported the use of drugs for migraine in the first trimester

Congenital malformations	Number of malformed infants		OR/RR[a] (95% CI)
	exposed to drugs for migraine	in population	
Any malformation	150	56 909	0.95 (0.80, 1.12)
Relatively severe malformation[b]	111	38 929	1.03 (0.85, 1.25)
Any chromosome anomaly	6	2 354	0.82 (0.20, 1.79)[c]
Any CNS malformation	7	1 407	1.83 (0.74, 3.78)[c]
Neural tube defect	2	454	1.59 (0.19, 5.73)[c]
Eye malformation	4	1 119	1.38 (0.38, 3.54)[c]
Ear malformation	9	2 870	1.15 (0.53, 2.18)[c]
Any cardiovascular defect	37	12 842	1.06 (0.76, 1.46)
VSD and/or ASD	24	6 799	1.27 (0.85, 1.90)
Orofacial cleft	3	2 201	0.51 (0.10, 1.48)[c]
Esophageal atresia	3	344	3.19 (0.88, 9.33)[c]
Small gut atresia	1	296	Not analysed
Anal atresia	1	465	Not analysed
Pylorostenosis	3	895	1.22 (0.25, 3.56)[c]
Hypospadias	6	3 489	0.63 (0.23, 1.38)[c]
Severe kidney malformation	4	730	1.96 (0.53, 5.02)[c]
Abdominal body defect	0	309	Not analysed
Diaphragmatic hernia	0	298	Not analysed
Poly/syndactyly	8	2 472	1.19 (0.51, 2.34)[c]
Limb reduction defect	3	683	1.48 (0.30, 4.32)[c]
Unstable hip, hip (sub)luxation	16	7 567	0.74 (0.45, 1.20)
Pes equinovarus	2	1 728	0.41 (0.05, 1.50)[c]
Craniostenosis	4	720	2.05 (0.51, 5.25)[c]

a OR adjusted for year of birth, maternal age, parity, smoking and body mass index.

b Includes all malformations with the exception of infants who have only one or more of the following diagnoses: preauricular appendix, tongue tie, patent ductus arteriosus at preterm birth, single umbilical artery, undescended testicle, unstable hip and nevus.

c RR as observed over expected numbers.

ASD = atrium septum defect; **OR** = odds ratio; **RR** = relative risk; **VSD** = ventricular septum defect.

Table IX. Congenital malformations among infants born to women who reported specific drugs for migraine in early pregnancy: comparison between ergots and triptans

Malformation group	Ergots		Triptans	
	number	OR/RR (95% CI)	number	OR[a] (95% CI)
Total number of infants	527		2777	
All malformations	21	0.80 (0.51, 1.25)	127	0.97 (0.81, 1.16)
Relatively severe malformations[b]	17	0.94 (0.57, 1.53)	92	1.04 (0.84, 1.28)
Any cardiovascular defect	7	1.22 (0.49, 2.51)[c]	29	1.00 (0.69, 1.44)
VSD and/or ASD	6	1.99 (0.73, 4.34)[c]	17	1.08 (0.67, 1.74)

a OR adjusted for year of birth, maternal age, parity, smoking and body mass index.

b Includes all malformations with the exception of infants who have only one or more of the following diagnoses: preauricular appendix, tongue tie, patent ductus arteriosus at preterm birth, single umbilical artery, undescended testicle, unstable hip and nevus.

c RRs as observed over expected numbers.

ASD = atrium septum defect; **OR** = odds ratio; **RR** = relative risk; **VSD** = ventricular septum defect.

one refers to unstable hip which is not regarded as a 'relatively severe malformation'.

Discussion

The advantage of the present study is the relatively large number of women who had used drugs for migraine during pregnancy and the possibility of studying and adjusting for putative confounders. Information on drug use was based on interviews performed in early pregnancy (thus prospectively in relation to pregnancy outcome) and on medical records or register information on prescriptions given during pregnancy. It is probable that not all drug use was identified. Women who had used drugs for migraine but were not recorded in the register were then regarded as unexposed. This is unlikely to affect risk estimates but will reduce the power of the study. Some women may have reported drug use that occurred outside the period of organogenesis, which will bias the risk estimates for malformations towards 1.0. The same effect was obtained if

Table X. Congenital malformations (any malformation) among infants born to women who reported use of specific drugs for migraine in the first trimester

Drug	Number malformed	Number exposed	OR/RR (95% CI)
Dihydroergotamine	5	135	0.78 (0.25, 1.81)[a]
Ergotamine combinations	16	388	0.82 (0.49, 1.36)
Sumatriptan	107	2257	0.99 (0.91, 1.21)
Naratriptan	1[b]	22	Not analysed
Zolmitriptan	12	362	0.76 (0.43, 1.35)
Rizatriptan	7	157	1.01 (0.40, 2.08)[a]
Almotriptan	1[c]	6	Not analysed
Eletriptan	3[d]	14	5.17 (1.07, 15.1)[a]
Pizotifen	3[e]	64	1.03 (0.21, 3.02)[a]

a RRs as observed over expected numbers.

b Congenital deformity of hand.

c Pulmonary artery stenosis + atrium septum defect.

d Ventricular septum defect/megacolon/unstable hip.

e Hydrocephaly/atrium septum defect/talipes calcaneovalgus.

OR = odds ratio; **RR** = relative risk.

women had received – and perhaps redeemed – prescriptions but had not used the drugs. Another weakness of the material is the lack of information on the actual amount of drug used.

The study was restricted to pregnancies that ended with delivery of an infant. There is thus a lack of information on induced abortions, performed after fetal diagnosis. This restriction is due to legislation in Sweden that prohibits the registration of induced abortions with identification data. This legislation makes it impossible to identify drugs used by women with pregnancies that ended in induced abortions, performed after fetal diagnosis. If a drug causes a malformation that is practically always identified and results in abortion (such as anencephaly) the system will not be able to detect the association. If it causes a malformation that sometimes, but not always, results in abortion (such as spina bifida), the association can still be identified but the power to detect it is reduced.

Fewer women used drugs for migraine after the first trimester than during the first trimester. One reason could be a fear of drug use during pregnancy, or another reason could be the often occurring decline in migraine intensity during pregnancy.[21]

Women who reported the use of migraine drugs in early pregnancy differed from other pregnant women in some aspects. Some of these could confound the analysis; notably maternal age, parity, and BMI. Adjustment for these variables and smoking were therefore made in the analysis. Further unidentified confounders could exist. For instance, no information on alcohol use exists in the register. The question of confounding by indication could be raised. In order to explain an absence of an effect of migraine drugs, a protective effect of migraine on delivery outcome must be supposed, which, however, is rather unlikely. The association between late use of drugs for migraine and an increased risk for pre-eclampsia and preterm birth could be explained by the underlying disease.

Women using drugs for migraine in early pregnancy also used many other drug categories in excess. Much of these can be explained by well known migraine co-morbidity.[22] An association between use of drugs for migraine and oral contraceptive failure is suggested in our material. Some of the concomitantly used drugs may influence delivery outcome. After exclusion of women who had used such drugs, the OR for pre-eclampsia and delivery induction decreased somewhat but remained statistically significant, while the increased risk for caesarean section disappeared.

No increased risk for bleeding around delivery was found after the use of drugs for migraine after the first trimester, which contrasts to the finding of an increased risk for atonic uterus and haemorrhage after the use of triptans.[5]

Little effect on the neonate was found. There was an increased risk for preterm births when drugs for migraine had been used after the first trimester but no certain effect on neonatal morbidity. There was no increased risk for a congenital malformation. For sumatriptan, this is in agreement with what is known from the literature. For other triptans, little information exists. There was a high risk for a malformation after maternal use of eletriptan but this was based on only three malformed infants among 14 exposed, and the three malformations differed in nature. Most likely this finding was random in spite of formal statistical significance but could warrant further investigation. The only previous study of eletriptan[5] had more early exposures (n = 179) but no specific information on congenital malformations were included in the report. In contrast to that study, we found no increased risk for stillbirths after the use of triptans.

There was no increased risk for congenital malformations after maternal use of ergotamine or dehydroergotamine. The risk estimate was actually below 1.0 but the number of exposures was limited (notably for dihydroergotamine) and the upper confidence limit for any congenital malformation after ergot exposure was 1.25, indicating that major teratogenicity is unlikely.

The question of whether migraine or drugs for migraine (notably ergots) can increase the risk for miscarriage cannot be studied directly with our data. It can be noted, however, that women reporting the use of drugs for migraine had no increased risk for previous miscarriages; this was also true for women who had used ergots.

Conclusions

Our analysis stresses the low risk associated with the use of drugs for migraine in pregnancy but associations with very rare malformations cannot be excluded. For triptans other than sumatriptan, data are still insufficient to exclude teratogenic effects but, to date, no data suggest that such effects exist.

Acknowledgement

This study was supported by a grant to Bengt Källén from the Evy and Gunnar Sandberg Foundation, Sweden. The authors' work was independent of the funders. None of the authors declared a conflict of interest.

References

1. Pfaffenrath V, Rehm M. Migraine in pregnancy: what are the safest treatment options? Drug Saf 1998; 19: 383-8
2. Fox AW, Chambers CD, Anderson PO, et al. Evidence-based assessment of pregnancy outcome after sumatriptan exposure. Headache 2002; 42: 8-15
3. Fox AW. Revised estimate for probability of successful outcome of pregnancy after sumatriptan exposure [letter]. Headache 2004; 44: 842-3
4. Cunnington M, Ephross S, Churchill P. The safety of sumatriptan and naratriptan in pregnancy: what have we learned? Headache 2009; 49: 1414-22
5. Nezvalová-Henriksen K, Spigset O, Nordeng H. Triptan exposure during pregnancy and the risk of major congenital malformations and adverse pregnancy outcomes: results from the Norwegian Mother and Child Cohort Study. Headache 2010; 50: 563-75
6. Heinonen OP, Sloane D, Shapiro A. Birth defects and drugs in pregnancy. Littleton (MA): Publishing Sciences Group, Inc., 1977
7. Källén B, Lygner P-E. Delivery outcome in women who used drugs for migraine during pregnancy with special reference to sumatriptan. Headache 2001; 41: 351-6
8. Bánhidy F, Puhó E, Czeizel AE. A possible dose-dependent teratogenic effect of ergotamine [letter]. Reprod Toxicol 2006; 22: 551-2
9. Bánhidy F, Árcs N, Horváth-Puhó E, et al. Maternal severe migraine and risk of congenital limb deficiencies. Birth Defects Res Part A Clin Mol Teratol 2006; 76: 592-601
10. Bánhidy F, Árcs N, Horváth-Puhó E, et al. Pregnancy complications and delivery outcomes in pregnant women with severe migraine. Eur J Obstet Gynecol Reprod Biol 2006; 134: 157-63
11. Bánhidy F, Ács N, Puhó E, et al. Ergotamine treatment during pregnancy and a higher rate of low birthweight and preterm birth. Br J Pharmacol 2007; 64: 510-6
12. Graham Jr JM, Marin-Madilla M, Hoefnagel D. Jejunal atresia associated with Cafergot ingestion during pregnancy. Clin Pediatr (Phila) 1983; 22: 226-8
13. Barkovitch AJ, Rowley H, Bollen A. Correlation of prenatal events with the development of polymicrogyria. AJNR Am J Neuroradiol 1995; 16: 822-7
14. Smets K, Zecic A, Willems J. Ergotamine as a possible cause of Möbius sequence: additional clinical observation. J Child Neurol 2004; 19: 398
15. Källén B. Drugs during pregnancy. New York: Nova Science Publishers, 2009
16. National Board of Health and Welfare, Centre for Epidemiology. The Swedish Medical Birth Register: a summary of content and quality [online]. Available from URL: http://www.socialstyrelsen.se/Publikationer2003/2003-112-3 [Accessed 2010 May 12]
17. Källén B, Otterblad Olausson P. Monitoring of maternal drug use and infant congenital malformations: does loratadine cause hypospadias? Int J Risk Safety Med 2001; 14: 115-9
18. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register: opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 2007; 16: 726-35
19. National Board of Health and Welfare, Centre for Epidemiology. Registration of congenital malformations in Swedish health registers [online]. Available from URL: http://www.socialstyrelsen.se/Publikationer2004/2004-112-1 [Accessed 2010 May 12]
20. Källén B. A birth weight for gestational age standard based on data in the Swedish medical birth registry 1985-1989. Eur J Epidemiol 1995; 11: 601-6
21. Torelli P, Allais G, Marizoni GG. Clinical review of headache in pregnancy. Neurol Sci 2010; 31, Suppl. 1: S55-8
22. Tietjen GE, Herial NA, Hardgrove J, et al. Migraine comorbidity constellations. Headache 2007; 47: 857-65

Correspondence: Professor *Bengt Källén*, Tornblad Institute, Biskopsgatan 7, SE-223 62 Lund, Sweden.
E-mail: Bengt.Kallen@med.lu.se