INVESTIGACIÓN ORIGINAL

SAFETY IN THE ACUTE MANAGEMENT OF MIGRAINE DURING PREGNANCY: A SYSTEMATIC REVIEW

Seguridad en el tratamiento de la migraña aguda durante el embarazo: una revisión sistemática

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Summary

Background. Migraine is three times more frequent in females than males and is modulated by changes in ovarian hormones throughout different stages of a female's life; migraine thus begins with the onset of menstruation, improves during the second and third trimester of pregnancy and a remission may sometimes be brought about during menopause.

Objetive. Evaluating the safety of acute management of migraine during pregnancy.

Materials and methods. A systematic review was made of the literature concerning observational analytical studies. A systematic search and selection was made of all analytical studies (cohort studies and cases and controls studies) regarding the acute management of migraine during pregnancy published between January 1966 and September 2007. The search covered the COCHRANE, MEDLINE, EMBASE and LILACS databases. Data were extracted using the PECOT strategy bearing in mind the intervention strategy, methodological quality and presence of greater or lesser congenital malformations related to the different medicaments used for the acute management of migraine.

Results. A total of 389 references were obtained of which 7 articles were selected by title and summary. Four articles complied with the inclusion criteria. No articles were found describing the risk of congenital malformations before being exposed to acetaminophen, anti-inflammatory agents non-steroidal, ergot alkaloids and/or opioids; just articles related to tryptans (specifically sumatryptan) were found.

Conclusions. Only data concerning the risk of congenital malformations arising from sumatryptan use was found regarding all the medicaments used for acute migraine attack, this being insufficient as the information was really poor and the studies had limitations, thereby making it difficult to make statements concerning their safety during pregnancy.

Key words: migraine disorders, pregnancy, sumatriptan, congenital abnormalities.

Ortiz P, Pinzón C, Gutiérrez A, Sobrino F. Safety in the acute management of migraine during pregnancy: a systematic review. *Rev.Fac.Med.* 2009; 57: 18-25.

Recibido:14/07/08/ Enviado a pares: 16/07/08/ Aceptado publicación: 13/02/09/

Resumen

Antecedentes. La migraña es tres veces más frecuente en mujeres que en hombres y está modulada por cambios fisiológicos en los niveles de hormonas ováricas, durante las diferentes etapas de la vida de la mujer. La migraña se inicia con la aparición de la menstruación, mejora durante el segundo y tercer trimestre del embarazo y remite con frecuencia durante la menopausia.

Objetivo. Evaluar la seguridad del tratamiento agudo de la migraña durante el embarazo.

Material y métodos. Se hizo una revisión sistemática de la literatura sobre estudios observacionales analíticos publicados entre enero de 1966 y septiembre de 2007. La búsqueda abarcó las bases de datos de COCHRANE, MEDLINE, EMBASE y LILACS. Los datos se obtuvieron mediante la utilización de PECOT teniendo en cuenta la estrategia de intervención, la calidad metodológica y la presencia de malformaciones congénitas relacionadas con los diferentes medicamentos utilizados para el tratamiento de la migraña aguda.

Resultados. Un total de 389 referencias se obtuvieron de los cuales siete artículos fueron seleccionados por el título y resumen. Cuatro artículos cumplieron con los criterios de inclusión. No se encontraron artículos que describen el riesgo de malformaciones congénitas antes de ser expuestos a acetaminofeno, antiinflamatorios no esteroideos, alcaloides del ergot y/o los opiáceos, sólo se encontraron artículos relacionados con triptanes.

Conclusión. Se encontró datos sobre el riesgo de malformaciones congénitas derivadas de la utilización del sumatriptan en relación con los medicamentos utilizados para el ataque agudo de migraña. La información fue escasa y los estudios tenían limitaciones, lo que hace difícil tener una guía sobre su seguridad durante el embarazo.

Key words: trastornos de jaqueca, embarazo, sumatriptan, anomalías congénitas.

Ortiz P, Pinzón C, Gutiérrez A, Sobrino F. Seguridad en el tratamiento de la migraña aguda durante el embarazo: una revisión sistemática. *Rev.Fac.Med.* 2009; 57: 18-25.

Introduction

Migraine is an incapacitating, chronic and paroxysmal neurovascular disorder which can begin at any age, affecting around 6 percent of males and 18 percent of females in the general population (1).

Ovarian hormones have a profound influence on females' central nervous system (CNS), modulating important neurotransmitter systems in different neurological disorders' physiopathology (1). Migraine is three times more frequent in females than males and is modulated by changes in ovarian hormones throughout different stages of a female's life; migraine thus begins with the onset of menstruation, improves during the second and third trimester of pregnancy and a remission may sometimes be brought about during menopause (2). Around 60-70 percent of patients suffering from migraine improve during pregnancy and 25 percent stay the same. It has been described that some females having no prior history of migraine may experience their first attacks during pregnancy (6). Some reported case series place greater emphasis on these patients presenting their first episode during pregnancy, as well as severe headache, they usually present transitory focal signs (migraine with aura) thereby requiring a deeper evaluation (2, 5, 6). Increased oestrogen levels during pregnancy has been proposed as being the potential mechanism explaining relief from migraine attack frequency and severity; however, this mechanism cannot explain the worsening or the appearance of new episodes

in some patients. The rapid fall in steroids may explain the increased incidence of episodes of migraine during inmediate postpartum. Females having a prior history of migraine more frequently present episodes of migraine during postpartum. Relief from migraine during pregnancy is independent of the action of suitable progesterone levels (2, 7).

Many medicaments may pass across the placenta thereby producing potentially adverse effects in the foetus. All things considered, most studies cannot therefore establish the safety of administering medicaments during pregnancy; however, it is thought that some are relatively safe (2).

Symptomatic treatment with non-steroid anti-inflammatories, acetaminophen alone or codeine, benzodiazepines, ergotamine, dehydroergotamine or tryptanes is used for reducing symptoms' severity and duration during acute migraine attacks in females in whom non-pharmacological treatment (repose, ice, massage and biofeedback) has been ineffectual (7).

However, in spite of knowing the pharmacological measures available, many questions face a doctor regarding which medicament should be chosen according to its safety during pregnancy. A systematic review was thus carried out aimed at preparing a tool providing greater support for combining the results of several studies examining the same question which could aid us in clarifying this controversy having such broad clinical importance.

Materials and methods

This was a systematic review designed in line with the methodology proposed by MOOSE (8). "How safe are the different medicaments used for acute management of migraine in pregnant females?" was the question which led to this review which was constructed using the PICOT strategy (9). Safe/safety was defined according to the measurements used in each article included in the review.

A systematic search and selection was made of all analytical studies regarding the acute management of migraine during pregnancy published between January 1966 and September 2007 (cohort studies and cases and controls studies). The search covered the COCHRANE, MEDLINE, EMBASE and LILACS databases, using combinations of the following MeSH terms: "Migraine Disorders"[MeSH] OR "Migraine Disorders/therapy"[MeSH] OR ("Migraine with Aura"[Mesh] OR "Migraine without Aura"[Mesh]) OR "Migraine Disorders/ Therapeutics"[MeSH] OR "Migraine Disorders/ Treatment Outcome"[Mesh]) OR "Headache"[MeSH] OR "Headache/ therapy"[MeSH]) OR "Headache/drug therapy"[MeSH]) OR "Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Barbiturates"[Mesh] OR "Antiemetics"[Mesh] OR "Ergot Alkaloids"[Mesh] OR "isometheptene «[Substance Name] OR "Pregnancy"[Mesh] AND "Tryptamines"[Mesh] OR "Acetaminophen"[Mesh] OR "Analgesics, Opioid"[Mesh AND "Pregnancy"[Mesh] OR ("Pregnancy Trimesters"[Mesh] OR "Pregnancy Trimester, Third"[Mesh] OR "Pregnancy Trimester, Second"[Mesh] OR "Pregnancy Trimester, First"[Mesh]).

Literature published in English, French and Spanish was the only limit established for the search. The search was done electronically; the titles and content of the summaries of the corresponding articles were analysed and the complete text of those considered pertinent were obtained and all the references presented in each article were reviewed. The following journals were manually

Table 1. *Evaluation criteria for the studies*

Studies were selected by outcome and the frequency of exposure to medicaments used in managing migraine during pregnancy if they dealt with the following topics:

1.	Pregnant females in any of the three trimesters of pregnancy;
2.	Observational descriptive studies (cohorts or cases and controls);
3.	A sample size having 10 or more cases;
4.	A prior or de novo diagnosis of migraine;
5.	Evaluating medicaments directed towards managing migraine (acetaminophen, Anti-Inflammatory Agents, Non-Steroidal, Ergot Alkaloids, opioids, tryptanes); and
6.	Identifying congenital malformations by categories or event.

consulted for identifying other relevant articles: Headache, Cephalalgia and Neurology. Studies reporting the adverse effects of the medicaments used for acute migraine attack during pregnancy were included (Table 1).

Studies were excluded which did not include relevant categorical measurements, case reports, summarised publications and studies of treatments still in the research phase. All studies were independently read by each of the current authors; any discrepancies were resolved by coming to a common agreement between the said authors. The following information was obtained from each article: the used criteria for diagnosing migraine, the patients' average age, the medicament and dose received, the sample size and outcomes measured in terms of greater and lesser malformations.

The data was set out in contingency tables in which the lines represented exposure (or not) to the medicaments and the columns represented the presence or absence of malformations.

Results

The results were presented according to the recommendations suggested in the *QUORUM* statement.10 Seven articles were initially (11-17) identified but only four of them (11,12,14, 17) fulfilled all the established criteria. The other three articles were excluded as they did not report the presence or absence of medicament-related congenital malformations (13,15) and for not having a control group (16). Articles were identified mentioning medicaments different to sumatryptan which were used for migraine during pregnancy. It was possible to obtain all the articles. Four studies published between 1999 and 2001 were included and analysed in depth (Table 2).

The four studies included provided data regarding 17,439 pregnant females of whom 864 had been exposed to some type of anti-migraine medicament (sumatryptan) during their gestation period and the newborn of 18 of them presented congenital malformations.

The studies which were included are now described. Kallen *et al*., compiled information from Swedish Board of Health records from 1st July 1995 to 30th June 1999. They only looked at exposure during the first trimester. The outcome studied was the presence or absence of congenital malformations as established by a paediatrician when evaluating the newborn at the moment of birth and entered as such in congenital malformation records.

They studied 905 births in females aged 19-45 who had reported using some medicament for

Table 2. *Study of the presence or absence of congenital malformations*

	TYPE OF STUDY	**Exposed n=658**	**Control group n=247**	**TOTAL**
Kellen *et al*., (2000)	Observational, Swedish Medical Birth Registry			
Malformations		18	10	28
No malformations		640	237	859
	TYPE OF STUDY	**Exposed n=76**	**Control group n=92**	**TOTAL**
O'Quinn *et al*., (1999)	Open label study, prospective			
Malformations		0	4	4
No malformations		67	73	140
	TYPE OF STUDY	**Exposed n=96**	**Control group n=192**	**TOTAL**
Shuhaiber *et al*., (1998)	Cohort, prospective			
Malformations		?	?	?
No malformations		?	?	?
	TYPE OF STUDY	**Exposed n=34**	**Not exposed n=89**	**TOTAL**
Olesen C *et al.*, (2000)	Retrospective, Danish Birth Registry			
Malformations		0	?	?
No malformations		0	?	?

migraine by itself or in combination during their first trimester of pregnancy (sumatryptan, dehydroergotamine, ergotamine+caffeine, ergotamine + caffeine + chlorcyclizine, pizotifen); 658 of them had been exposed to sumatryptan alone or in combination.

Twenty-eight congenital malformations were described, 18 of which had occurred in the group exposed to sumatryptan (2.7%) (1.6-4.3 95%CI).

The malformations were classified into being greater and/or lesser; 16 infants were described as having greater malformations. 12 had only been exposed to sumatryptan in combination (ergotamine). 12 lesser malformations were described; 6 had been exposed to sumatryptan by itself or in combination (dehydroergotamine), 2 combined with ergotamine, 2 dehydroergotamine and 1 pizotifen.

However, the magnitude of the influence of taking other medicaments used for migraine could not be established; even when they were not specific for this (Beta-blockers, anti-inflammatories, muscle relaxanis, analgesics, anti-epileptics, sedatives, anti-depressives, anti-asthmatics, anti-histaminics and antacids), the article only stated that the babies of the 3 patients exposed to anti-epileptics had not suffered malformations.

O'Quinn *et al*., carried out an analytical prospective study which included 12,339 patients having migraine criteria; 9,686 of them were female and there were 168 documented pregnancies regarding this group. Sumatryptan injections were provided for acute treatment of migraine during one-year followup. The results from 92 females who consumed tryptans before becoming pregnant and 76 during their pregnancy were compared (75 during the first trimester of

pregnancy and 1 in both first and second trimesters of pregnancy). Seventy-three of the 92 females exposed before conception had healthy children and 11 had spontaneous abortions. Other abnormalities found were 1 ectopic implant, 1 was still-born (*abruptio placentae*) and 4 had lesser congenital malformations (2 patients chose to have an abortion).

Sixty-seven of those exposed after conception had a normal perinatal result, 8 presented spontaneous abortion and 1 had an ectopic implant. No still-born or lesser congenital malformations were documented.

Shuhaiber *et al*., carried out a multi-centre analytical prospective study comparing pregnant patients suffering from migraine exposed to sumatryptan to two control groups; one might have been treated with other drugs for managing migraine and the other group received no medicament whatsoever. Ninety-six of the 288 pregnant females evaluated were exposed to sumatryptan during pregnancy (95 pregnant females during the first trimester of pregnancy, 12 of whom remained exposed during the second trimester and 6 during the third trimester and just 1 patient was exposed during the second and third trimesters). Fifty-seven females reported using the medicament just once during pregnancy and 38 females reported repeated use of the medicament during pregnancy.

The control groups consisted of 96 females being exposed to other medicaments for migraine (acetaminophen, non-steroid anti-inflammatories and narcotic analgesics) and 96 females were not exposed to any type of teratogenic medicament.

The information presented in this article's text and tables is inconsistent and does not present data regarding the findings but rather as RR which are not statistically significant (RR=1.05 and RR=1.06 between the group exposed to sumatryptan compared to the non-teratogenic group, i.e. exposed to other drugs).

Olesen C *et al.*, took patients from The Danish Medical Birth Registry 1991-1996. They evaluated a group of 34 cases of females exposed to sumatryptan during pregnancy (they did not specify whether exposure time had been during the whole pregnancy or during a determined trimester) and a control group of 89 females suffering migraine who had not taken taking an anti-migraine medicament for the previous months before pregnancy or during pregnancy and a group of 15,995 healthy females who had received no medication whatsoever during pregnancy.

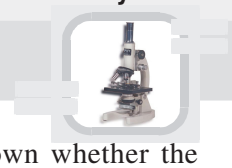
No congenital malformations were reported for the 34 females exposed to sumatryptan; this information was not given for the control group.

Discussion

The literature contains controversies concerning the use of medicaments for acute migraine attack during pregnancy and the risk of developing congenital malformations.

Articles state that most patients do not require pharmacological treatment, but there is a small group which does not improve with non-pharmacological means (7).

It is difficult for doctors to decide on the medicament to be administered given that many may pass across the placenta thereby producing potentially adverse effects on the foetus. Most studies thus cannot definitively establish the safety of administering medicaments during pregnancy; however, it is believed that some are relatively safe.



The data used in this study was taken from research based on a cases and controls or cohorts design. A systematic review of observational studies has limitations due to the presence of factors regarding confusion, bias or both.

Only studies evaluating the use of tryptans during pregnancy (specifically sumatryptan) were found.

People exposed to sumatryptan could differ in the presence of other factors which could be relevant for the risk of developing greater and/or lesser congenital malformations (i.e. family antecedents, other systemic diseases, progenitors' environmental or work-based exposure, socioeconomic level, the parents' ages, nutritional deficiencies, the number of prior pregnancies or consuming other non-specific medicaments for migraine).

Even though known confusion factors may be controlled, some degree of residual confusion may be found, even more so when these cannot be measured with sufficient precision (this being very common in these types of epidemiological studies). Confusion factors represent the greatest threat to the validity of cohort studies' results.

Medicaments administered during pregnancy can produce spontaneous abortion, teratogenicity, abnormalities in foetal growth, perinatal effects, abnormalities in postnatal development, the development of oncogenesis and behavioural and functional changes (7). Most studies only evaluate malformations in live newborn and do not contemplate abortions; only O'Quinn and Shuhaiber's studies described them, finding no differences between females exposed and not exposed to sumatryptan. However, this information remains insufficient as the latter study cites a number of elective abortions, regarding which it is unknown whether the females had been given a diagnosis of some malformation, thereby leading to them choosing abortion. It is important for future studies that the reason determining whether to proceed with an abortion is made known as this could be due to some congenital malformation having been diagnosed or consist of an elective abortion in those countries where it is permitted.

It is also important for future studies that information regarding the follow-up time for the newborn be available for detecting congenital malformations. Some studies recommend a minimum 4-year follow-up, such period being necessary for identifying the maximum number of congenital malformations (12).

The adverse effects of medication during pregnancy depend on the dose and the administration route as well as the relative exposure time during the development period. In spite of this, only O'Quinn's study specified the dose and administration route, but none of the studies described the duration of exposure time.

The studies evaluated here differed in their methodology and the way the data was reported. Kallen and Shuhaiber's studies described malformations in the group exposed to sumatryptan, this not being clear in Shuhaiber's study. Olessen and O'Quinn's studies did not find malformations, but this could have been due to the sample size or possible under-recording of malformations.

Regarding all the medicaments used for acute migraine attack, data was only found concerning the risk of congenital malformations with sumatryptan. This was still insufficient given that the information really is poor and the studies have limitations, meaning that it is difficult to affirm its relative safety during pregnancy.

Conflict of interest

The authors declare not conflict of interest.

Acknowledments

We like to thank Oscar Gamboa at the Clinical Research Unit of the National Cancer Institute of Colombia for their help to define and work out the search strategy of this systematic review.

References

1. **Van de Ven RC, Kaja S, Plomp JJ, Frants RR, Van den Maagdenberg AM, Ferrari MD.** Genetic models in migraine. *Arch Neurol.* 2007; 64:643-646.
2. **Loder EW.** Menstrual migraine: pathophysiology, diagnosis and impact. *Headache*. 2006; 46 [Suppl 2]:S55-S60.
3. **Stewart WF. Lipton R. Silberstein S.** Menstrual cycle and headache in a population sample of migraineurs. *Neurology.* 2000; 55: 1517-1523.
4. **Wright DS, Patel MK.** Focal migraine and pregnancy. *BMJ.* 1986; 293: 1557-1558.
5. **Chancellor MD, Wroe SJ.** Migraine occurring for the first time in pregnancy *Headache.* 1990; 30: 224-227.
6. **Stein GS.** Headaches in the first postpartum week and their relationship to migraine. *Headache.* 1981; 21: 201-205.
7. **Silberstein SD, Goadsby PJ, Lipton RB.** Migraine: Diagnosis and treatment In *Headache in Clinical Practice,* pp 193-194. Isis Medical Media, Oxford 1998.
8. **Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al.** Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) Group. *JAMA.* 2000;283:2008-12.
9. New Zealand Guidelines Group Incorporated. Handbook for the preparation of explicit Evidence-based Clinical Practice Guidelines [Internet]. Wellington: NZGG; November 2001. [accessed on 26th April 2005]. Available at: http://www.nzgg.org.nz/download/files/nzgg_guideline_handbook.pdf.
10. **Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF.** Improving the quality of reports of meta-analyses of randomised controlled trials: the QUORUM statement. Rev Esp Salud Publica. 2000; 74:107-118.
11. **Kàllén B, Lygner PE.** Delivery outcome in woman who used drugs for migraine during pregnancy with special reference to sumatriptan. Headache. 2001;41: 351-356.
12. **Olesen C, Steffense FH, Sorensen HT, Nielsen GL, OlseN J.** Pregnancy outcome following prescription for sumatriptan. Headache 2000;40: 20-24.
13. **Maggioni F, Alessi C, Maggino T, Zanchin G.** Headache during pregnancy. Cephalalgia. 1997; 17:765-769.
14. **Shuhaiber S, Pastuszak A, Schick B, Matsui D, Spivey G, Brochu J, et al.** Pregnancy outcome following first trimester exposure sumatriptan. Neurology. 1998;51:581-583.
15. **Aromaa M, Rautava P, Lelenius H, Sillanpaa ML.** Pre-pregnancy headache and the well-being of mother and newborn. Headache. 1996;36:409-415.
16. **Reiff-Eldridge R, Heffner CR, Ephross SA, Tennis PS, White AD, Andrews EB.** Monitoring pregnancy outcomes after prenatal drug exposure through prospective pregnancy registries: A pharmaceutical company commitment. Am J Obstet Gynecol. 2000;182:159-163.
17. **O´Quinn S, Ephross A, Williams V, Davis RL, Gutterman DL, Fox AW.** Pregnancy and perinatal outcomes in migraineurs using sumatriptan: a prospective study. Arch Gynecol Obstet. 1999;263: 7-12.
18. **Fox AW, Chambers CD, Anderson PO, Diamond ML, Spierings EL.** Evidence-based assessment of pregnancy outcome after sumatriptan exposure. Headache. 2002;42:8-15.