

Systematic Review: Is the Use of NSAIDs Safe During Pregnancy in Women With Rheumatic Disease?

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Objective: To analyze the security of non-steroidal anti-inflammatory drugs (NSAID) in rheumatic disease patients during pregnancy.

Methods: We performed a systematic review using a sensitive search strategy. All studies published in MEDLINE (since 1961), EMBASE (since 1961), and Cochrane Library (up to January 2008) were selected. We defined the population (pregnant women 16 years or above with a musculoskeletal disease), the intervention (use of NSAID), and the outcomes related to safety (number of live births, stillbirths, length of gestation and of labour, birth-weight, number and type of congenital malformations). The titles and abstracts of articles retrieved from the search were reviewed and high quality cohorts and case-control studies were included.

Results: Of a total of 149 references retrieved, only 8 were analyzed in detail, and 3 were finally included. More than 2600 pregnant patients were analyzed. There are many different NSAIDs as well as many different outcomes. Different NSAID were included as well as different outcomes. There was no increased risk of congenital malformations in 2 of the studies. In the third one there was an increased risk for cardiac malformations (OR=1.86; 95% CI, 1.32-2.62) and orofacial clefts (OR=2.61; 95% CI, 1.01-6.78).

Conclusions: There is not enough information to support the negative effects of NSAIDs during pregnancy. On the other hand there is one study suggesting that the use of NSAIDs could increase the risk of cardiac and orofacial malformations in newborns, therefore these drugs should be used with caution.

Key words: Non-steroidal anti-inflammatory drugs. Pregnancy. Congenital malformation.

Revisión sistemática: ¿es seguro el uso de AINE durante el embarazo en mujeres con afección reumática?

Objetivo: Analizar la seguridad del tratamiento con antiinflamatorios no esteroideos (AINE) en embarazadas con afección reumática.

Métodos: Revisión sistemática. Se definió una estrategia de búsqueda bibliográfica sensible en MEDLINE (desde 1961), EMBASE (desde 1980) y Cochrane Library (hasta enero de 2008); se definió la población (mujeres embarazadas mayores de 16 años con enfermedad reumática) y la intervención (tratamiento con AINE); se midió, como resultados, el número de recién nacidos vivos, las pérdidas fetales, la duración de la gestación y del parto, el peso del recién nacido y número y tipo de malformaciones congénitas. Se revisaron, por título y resumen, los artículos recuperados de la búsqueda y se incluyeron estudios de cohortes y de casos y controles.

Resultados: De un total de 149 artículos rescatados, se seleccionaron 8 para lectura en detalle, de los que finalmente se seleccionaron 3, que incluyeron a más de 2.600 pacientes embarazadas. Destaca la gran variedad en el tipo de AINE y en las medidas de desenlace. En 2 de los artículos no se encontró un aumento del riesgo de malformaciones, mientras que en el tercero se observó un aumento del riesgo de malformaciones cardíacas (*odds ratio* [OR] = 1,86; intervalo de confianza [IC] del 95%, 1,32-2,62) y orofaciales (OR = 2,61; IC del 95%, 1,01-6,78).

Conclusiones: No hay suficientes datos de que no sea seguro el uso de AINE durante el embarazo. Por otro lado, un estudio apunta que la utilización de AINE podría relacionarse con un discreto aumento en la frecuencia de malformaciones cardíacas y orofaciales, por lo que es aconsejable usar estos fármacos con precaución en el embarazo.

Palabras clave: Antiinflamatorios no esteroideos. Embarazo. Malformación congénita.

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Introduction

The use of non-steroidal anti-inflammatory drugs (NSAID) is very frequent in patients with rheumatic disease.¹ The exposure to these drugs is common during the first trimester of pregnancy in spite of them being classified as a category C or D (when administered in the thirds trimester).² It has been reported that the use of NSAID in the final stages of pregnancy leads to the premature closure of the ductus arteriosus³ and, on the kidney, leads to oligohydramnios and neonatal anuria.⁴ Due to these effects, the use of NSAID during the third trimester of pregnancy is contraindicated. However, little is known about the possible teratogenic effects and if the benefit of their use in the first trimester overcomes the risks. This causes, when a patient with inflammatory disease becomes pregnant, the treatment for arthritis to become a challenge for her physician. The suspension of NSAID can lead to an inflammatory flare which may be difficult to control only with analgesia. Normally, patients with rheumatoid arthritis improve with pregnancy, but sometimes this improvement is delayed until the second or third trimester.⁵ Occasionally, if oligoarticular affection is exclusively the problem, only NSAID can control the symptoms. For this reason they are commonly employed during the first trimester. Due to the risk that these drugs can represent in pregnancy there is very little information on the use of NSAID in pregnant women with rheumatic disease. With this systematic review we attempt to determine if INSAID can be used safely in this group of patients.

Methods

A systematic review was carried out to analyze the safety of the use of NSAID in pregnant women. The selection criteria for the study were:

1. Studies that included pregnant patients over 16 years of age with rheumatic disease.
2. Studies in which the patients received NSAID. There was no restrictions on the type and dose, but studies in which the subjects received antiplatelet dosages (non-analgesic or anti-inflammatory) were excluded, as well as topical treatments. Studies in which the patients employed NSAID as tocolytic or in the postpartum were also subject to exclusion.
3. In order to evaluate safety, studies that analyzed one of the following variables were included: number of live-born products and fetal losses, duration of gestation and labor, weight at birth and congenital malformations.
4. In relation to the design of the studies, clinical trials (CT), cohort studies and case-control studies were included. Studies in healthy volunteers and animals were excluded. Finally, articles in both spanish and english were selected.

The following databases were searched until January 2007: MEDLINE (from 1960), EMBASE (from 1980), and the Cochrane Library (Central). Both MeSH and free text terms were searched. No limits were given regarding the publication date. The search strategy is detailed in Table 1. The search did not include abstracts from national (SER) or international (ACR, EULAR) meetings given the volume of articles recovered from the database search. A single reviewer analyzed the resulting articles and performed the detailed analysis of the included documents. The result of this search, first, was thinned by title and abstract or the complete article in those cases in which no abstract was available. After this process, the remaining articles, the remaining articles were analyzed in detail. Finally, a manual search with the references of the selected articles was carried out for their detailed analysis. All of the references were downloaded from the internet and introduced into the Procite 5.1 software program to ease their management. To assign methodological quality to the included studies, a level of evidence score proposed by Oxford⁶ was employed for the cohort and case-control studies.

Results

The results of the search are detailed in Figure. Three studies with more than 2600 pregnant patients were finally

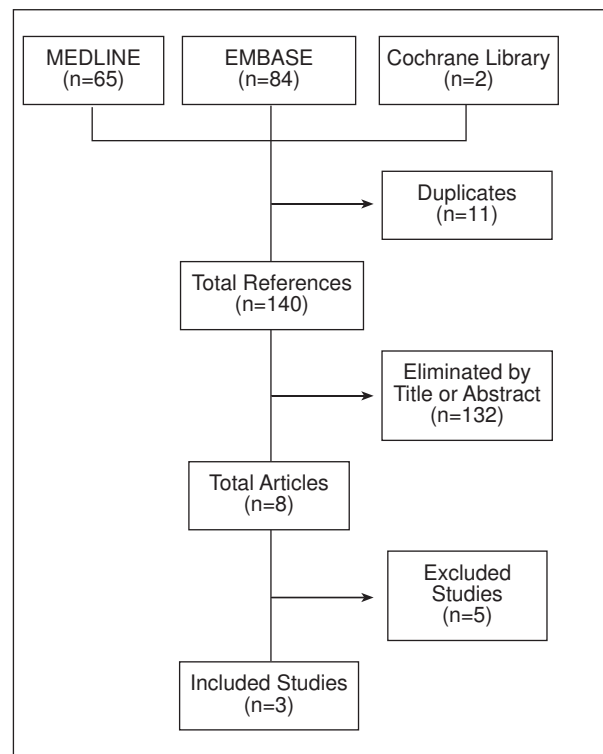


Figure. Flow of the study selection.

TABLE 1. Search Strategies and Results on MEDLINE

Search Strategy	Results
1 (((((((((((("Pregnancy"[MeSH] OR "Pregnancy Trimester, Third"[MeSH] OR "Pregnancy Trimester, Second"[MeSH] OR "Pregnancy Trimester, First"[MeSH] OR "Pregnancy Trimesters"[MeSH])) OR (("Pregnant Women"[MeSH]))) OR (("Pregnancy, High-Risk"[MeSH] OR "Pregnancy, Ectopic"[MeSH] OR "Pregnancy Outcome"[MeSH] OR "Pregnancy Complications"[MeSH] OR "Pregnancy, Tubal"[MeSH] OR "Pregnancy, Prolonged"[MeSH] OR "Pregnancy, Multiple"[MeSH] OR "Pregnancy, Abdominal"[MeSH] OR "Pre-Eclampsia"[MeSH])) OR (("Fetus"[MeSH] OR "Maternal-Fetal Relations"[MeSH])) OR (("Prenatal Care"[MeSH])) OR ((pregnanc*[tiab] OR pregnant*[tiab])) OR ((fetus[tiab] OR foetus[tiab])) OR ((prenatal*[tiab] OR antenatal*[tiab] OR antepart*[tiab])))	704 835
2 NSAID OR Nonsteroidal Anti-Inflammatory Agents OR Nonsteroidal Antiinflammatory Agents OR Analgesics, Anti Inflammatory OR Non-Steroidal Anti-Rheumatic Agents OR Non-Steroidal Antirheumatic Agents OR Aspirin-Like Agents OR Agents, Aspirin-Like OR naproxen* OR ibuprofen* OR dexibuprofen OR dexketoprofen OR flurbiprofen OR Ketoprofen OR Ketorola* OR aceclofenac OR diclofenac OR lornoxicam OR meloxicam OR piroxicam OR tenoxicam OR indometacin OR sulindac OR tolmetin OR fenilbutazon OR Phenylbutazone OR nabumeton OR celecoxib OR etoricoxib OR parecoxib OR rofecoxib OR valdecoxib OR lumiracoxib OR salicylic acid OR acetylsalicylic acid OR diflunisal OR Cyclooxygenase 2 Inhibitors OR COX-2 Inhibitors OR COX2 Inhibitors, OR Coxibs	157 408
3 1 and 2	5503
4 (Musculoskeletal diseases OR Polymyalgia Rheumatica OR Lupus Erythematosus, Systemic OR vasculitis OR polymyositis OR dermatomyositis) OR (musculoskeletal diseases [tiab] OR polymyalgia[tiab] OR "lupus erythematosus systemic" [tiab] OR vasculitis[tiab] OR polymyositis[tiab] OR dermatomyositis[tiab])	742 806
5 3 and 4	367
6 acute [All Fields] OR post-operative [All Fields] OR post-surgical[All Fields] OR postsurgical [All Fields] OR Postoperative Complications [MeSH] OR Intraoperative Complications [MeSH] dysmenorrhoea[All Fields] OR orthodontic [All fields] OR Cancer OR neoplasm OR cancers OR tumor OR tumors OR Benign Neoplasms OR metastasis OR metastases	2 290 508
7 5 NOT 6	326
8 7, Limits: Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, English, Spanish	65

included. A great deal of variety is observed regarding the NSAID employed, 2 cohort studies (2b quality) and 1 case control study (3a quality) were included. Most of the studies included patients with osteoarthritis (OA), systemic lupus erythematosus (SLE), psoriatic arthritis (PSA), or rheumatoid arthritis (RA). The main results from the included studies are described next (Table 2).⁷⁻⁹ The list of excluded articles, as well as the reason for their exclusion, are detailed in Table 3.¹⁵⁻¹⁹

Main Results of the Cohort Studies

In the study by Lewis et al⁷ the duration of pregnancy is measured, as well as the duration of labor and hemorrhaging produced by labor in 3 different groups of patients. The first are patients with rheumatic disease exposed to a dose of aspirin (ASA) >3 g/day for the last 6 months of pregnancy. The second group is formed by patients with rheumatic disease who did not use NSAID and the third by healthy pregnant women who were not exposed to these drugs. They observe that in patients exposed to high doses of ASA, the mean duration of pregnancy is a week longer than those unexposed. Forty-two per cent of the patients who take ASA have pregnancies over 42 weeks. The mean duration of labor

is 5 h longer than unexposed patients. No differences are seen in the mean weight of the newborn between exposed and unexposed pregnant women with rheumatic disease, but there is a difference when compared to the children of healthy subjects. Another difference seen is the loss of a larger mean amount of blood during labor in the exposed group.

The study by Østensen et al⁸ included patients in 2 periods. In the first they gather data from 45 patients and in the second one they add 43. Then they divide the total in 2 groups, exposed to NSAID and unexposed. Standard doses are used, except in the case of ibuprofen and salicylates, which are less. The drug which was most employed was naproxen (51%). In the third trimester, 71% took NSAID and in the second 58%, and the third 38% of patients. There were 2 fetal losses, one in each group. No differences were seen when comparing the rate of preterm birth in exposed and unexposed subjects. The mean duration of gestation was the same in both groups, 38.6 weeks. There were no statistically significant differences when comparing the length of labor in both groups, nor when comparing the mean weight at birth from both groups. In the group of exposed subjects, 3 (6%) cases of preeclampsia were seen, while 2 (4%) cases were seen in the non-exposed. With respect to hemorrhage during labor, 2 cases, one in each group, were seen. Two

TABLE 2. Characteristics of the Included Studies^a

Study	Participants and Intervention	Results
Ericson et al ⁹ (2001), case control study (Sweden). Quality 3b	2487 mujeres (2557 children) exposed to NSAID. Cases: 40 children with cardiac malformations in mothers exposed to NSAID in the first trimester. Controls: 40 children with no defects in mothers exposed to NSAID. Type of rheumatic disease is indicated in 14 cases and 18 controls. Age at pregnancy: 19-44 years	Total rate of malformations: OR=1.04; 95% CI, 0.84-1.29. Cardiac malformations (1.6%), among them septum defects (57.5%). Ibuprofen: 1129 exposed, 15 children with malformations (1.3%). Naproxen: 918 exposed, 14 malformations (1.5%). Diclofenac: 574 exposed, 8 malformations (1.4%)
Lewis et al ⁷ (1973), retrospective cohort study (USA). Follow-up 20 years. Quality 2b	103 patients exposed to ASA >3.25 g in months 4-9 of pregnancy. Group I: exposed to ASA with rheumatic disease (n=103). Group II: non exposed with rheumatic disease (n=52). Group III: healthy non exposed (n=50). Mean age 26 (5.68) years	Increase in the duration of pregnancy in exposed patients (42%, more than 42 weeks). Increase in the duration of labor (70% longer). Increase of the mean hemorrhage during labor in patients exposed. Reduction in weight at birth in exposed patients
Østensen et al ⁸ (1996), prospective cohort study (Norway). Quality 2b	88 exposed patients (94 pregnancies). Group I: exposed to NSAID, 45 (49 pregnancies). Group II: not exposed to NSAID, 43 (45 pregnancies). Mean age, 28.4 years. Mean duration of disease, 8.6 years	Live born, 92. Fetal losses, 2. Congenital malformations, 2 in non exposed subjects. No increase in the length of pregnancy. No increase in the duration of labor. No weight reduction in the newborn. No increase in hemorrhaging that required transfusion

^aASA indicates acetyl salicylic acid; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio.

TABLE 3. Excluded Studies and Reasons for Exclusion

Study	Cause of Exclusion
Correy et al ¹⁸ (1991)	Patients exposed to NSAID during pregnancy, without rheumatic affection
Kozer et al ¹⁵ (2002)	Patients exposed to ASA during the first trimester of pregnancy, but without rheumatic affection
Li et al ¹⁶ (2003)	Patients exposed to NSAID since the last menstruation until week 20 of pregnancy, without rheumatic disease
Nielsen et al ¹⁷ (2001)	Pregnant patients taking NSAID from 30 days before conception to labor. Without rheumatic disease
Pons et al ¹⁹ (1996)	Clinical case

cases of congenital malformations (Turner's syndrome and Down's syndrome) were seen in the non-exposed group.

Main Case-Control Studies

Ericson et al⁹ divided their study into 2 parts. On one hand, they compared the rate of malformations in the children of mothers exposed to NSAID and that expected in the population, without noting differences. However, there was an increase in the number of cardiac malformations (odds ratio [OR] = 1.86; 95% confidence

interval [CI], 1.32-2.62). Of the newborns of mothers (n=1129) who took ibuprofen, 15 (1.3%) presented malformations. Among the 918 patients exposed to naproxen, 14 (1.5%) children had cardiac defects. Of 574 patients who used diclofenac, 8 (1.4%) children were born with cardiac malformations. These proportions do not differ significantly. They also detected 6 children with cleft lip. In these cases, 5 of the mothers had received naproxen (OR=2.61; 95% CI, 1.01-6.78) and 1, ibuprofen. Then they decided to search for malformations associated to each NSAID, carrying out a case-control study, localizing 40 women exposed to NSAID and whose children had a cardiac defect and selected 40 controls (without malformations) between women exposed to NSAID. Of the cardiac malformations that appeared, 23 are ventricular or atrial septum defects or a combination of both (58%). In 8 (20%) cases the type of malformation was not specified. In these cases there did not seem to be any relation to NSAID.

Discussion

NSAID are used with frequency in patients with rheumatic disease. When studying their effect on pregnancy we found that most of the information we have comes from animal studies.¹⁰⁻¹² In humans, indomethacin and salicylates are the most commonly studied drugs.^{13,14} Of the rest, very few studies in pregnant women have been done. NSAID are used mostly in the first and second trimester of pregnancy, mainly due to 2 reasons: *a)* the patients who are taking the drug for this diseases and continue to do

so until discovering they are pregnant; and *b*) normally, those who keep taking them feel less need to use them in the third trimester due to the frequency of improvement or remission of these diseases in said trimester.

In this article we analyzed the safety results for the use of NSAID for the treatment of rheumatic disease in pregnant women through a systemic review of literature. The objective is to contribute to the published scientific evidence when generalizing or reaching a consensus on the use of NSAID in pregnant women. In the study by Østensen et al,⁸ in contrast to what has been observed in animals, no increase in the duration of pregnancy or labor was seen. In the results of the study by Lewis et al,⁷ there was a significant increase in the duration of both. Lewis et al⁷ also observed an increase in hemorrhage during labor, something not seen by Østensen et al.⁸ Both studies see a reduction in the weight of the products of mothers exposed to NSAID. Here it appears as a confusion factor of the severity of the disease, something that does not appear in any of the 2 studies mentioned, preventing us from making a stratified analysis.

Regarding teratogenesis, while Østensen et al⁸ did not find evidence for it in these patients, Ericson et al⁹ observed an increase in cardiac malformations. This study did not find a specific association between a concrete NSAID and cardiac malformations. These could be due to a general effect of NSAID or due to some underlying disease that acts as a confusion factor.

A problem seen by Ericson et al⁹ and Østensen et al⁸ is the lack of data on time of exposure and dose employed. In the included studies, there are 3 that do not refer to osteomuscular pain, but do give information on the use of NSAID in pregnancy. Because they are of a better quality than the studies included, they are described here in order to amplify the information at hand.

Kozer et al¹⁵ perform a systematic review of the literature in which the search for data on the teratogenesis of ASA during the first trimester of pregnancy. The global rate of malformations is not elevated in children of exposed mothers, However, the studies are heterogeneous, with different ways of detecting malformations and the variety of ages in which these defects were observed. When analyzing the risk of malformations of the central nervous system, this was not elevated as compared to controls. Regarding cardiac malformations, no elevated risk is seen when compared to controls. In children with cleft lip they found an increase in the risk of children of exposed mothers (OR=2.87; 95% CI, 2.04-4.02). They also observed an increase in the risk of gastroschisis (OR=2.87; 95% CI, 1.44-3.88).

Li et al¹⁶ published the results of a prospective cohort in which prenatal exposure to NSAID, ASA or paracetamol was evaluated to determine if an association with an increased risk of spontaneous abortion. They detect an increased risk of abortion when NSAID and ASA were used closer to the time of conception (OR=5.6; 95% CI,

2.3-13.7) or when employed for over a week during the first trimester (OR=8.1; 95% CI, 2.8-23.4). No increase in the risk was seen with the use of paracetamol, independent of the moment of exposure.

Lastly, Nielsen et al¹⁷ performed 2 studies, one of cohorts and another of cases and controls. In both they searched for malformations and the risk of spontaneous abortion. In the cohort study they observed 46 (4.2%) malformations in 1106 pregnancies of women who took NSAID during the first trimester of pregnancy, compared to 564 (3.3%) in 17 259 pregnancies in the reference cohort (adjusted OR = 1.27; 95% CI, 0.93-1.75). Adjusted OR for low weight and preterm birth in exposed women were, respectively, 0.79 (95% CI, 0.45-1.38) and 1.05 (95% CI, 0.8-1.39). There was no significant association. In the case control study there was an observed increased risk of spontaneous abortion in exposed patients, which increased when this exposure was closer to the time of conception.

Conclusions

This review shows the scarcity of data on the safety of the use of NSAID during pregnancy. Data obtained in women with rheumatic disease exposed to NSAID, although indicative of an increase in cardiac and orofacial malformations, is not conclusive due to the low level of evidence on the included articles. In studies performed in women exposed to these drugs, who did not have rheumatic diseases, no increase in cardiac malformations is evident, although there is an increase in orofacial malformations, gastroschisis and spontaneous abortion. Faced with the lack of conclusive data, the use of NSAID should be restricted during pregnancy.

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