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 1980), 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.
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 third 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 arteriosus\(^3\) 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 NSAID 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 bith 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 Oxford\(^6\) 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
TABLE 1. Search Strategies and Results on MEDLINE

<table>
<thead>
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<th>Search Strategy</th>
<th>Results</th>
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| 2 NSAID OR Nonsteroidal Anti-Inflammatory Agents OR Nonsteroidal Anti-inflammatory Agents OR Analgesics, Anti-inflammatory OR Non-steroidal Anti-Rheumatic Agents OR Non-steroidal Anti-rheumatic Agents OR Aspirin-like Agents OR Agents, Aspirin-like OR naproxen* OR ibuprofen* OR dexibuprofen OR dextroprofen OR flurbiprofen OR Ketoprofen OR Ketorolac* OR acetosalicylic OR diclofenac OR lornoxicam OR meloxicam OR indomethacin OR 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 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 al 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

Main Results of the Cohort Studies

In the study by Lewis et al 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 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 al 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
cases of congenital malformations (Turner’s syndrome and Down’s syndrome) were seen in the non-exposed group.

Main Case-Control Studies

Ericson et al. 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 selecting 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. In humans, indomethacin and salicylates are the most commonly studied drugs. 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Cause of Exclusion</th>
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<tbody>
<tr>
<td>Correy et al. (1991)</td>
<td>Patients exposed to NSAID during pregnancy, without rheumatic affection</td>
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<tr>
<td>Kozer et al. (2002)</td>
<td>Patients exposed to ASA during the first trimester of pregnancy, but without rheumatic affection</td>
</tr>
<tr>
<td>Li et al. (2003)</td>
<td>Patients exposed to NSAID since the last menstruation until week 20 of pregnancy, without rheumatic disease</td>
</tr>
<tr>
<td>Nielsen et al. (2001)</td>
<td>Pregnant patients taking NSAID from 30 days before conception to labor. Without rheumatic disease</td>
</tr>
<tr>
<td>Pons et al. (1996)</td>
<td>Clinical case</td>
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ASA indicates acetylsalicylic acid; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio.

TABLE 3. Excluded Studies and Reasons for Exclusion
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, 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, there was a significant increase in the duration of both. Lewis et al also observed an increase in hemorrhage during labor, something not seen by Østensen et al. 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 al did not find evidence for it in these patients, Ericson et al 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 al and Østensen et al 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 al 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 al 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 al 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.

References