Safety of Pain Therapy During Pregnancy and Lactation in Patients with Inflammatory Arthritis: A Systematic Literature Review

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ABSTRACT. ***Objective.*** To systematically review the safety of various pain therapies used during pregnancy and lactation in patients with inflammatory arthritis.

Methods. A systematic literature review was performed in Medline, Embase, the Cochrane Library, and the American College of Rheumatology/European League Against Rheumatism 2008-2009 meeting abstracts, as part of the multinational 3e (Evidence, Expertise, Exchange) Initiative for generating practical recommendations about Pain Management by Pharmacotherapy in Inflammatory Arthritis. Articles fulfilling predefined inclusion criteria were reviewed, and quality appraisal was performed.

Results. The search yielded a total of 3974 articles and 7 abstracts. The only study that fulfilled the criteria for pain therapies in pregnancy was a systematic review published in 2008, evaluating the effects of nonsteroidal antiinflammatory drug (NSAID) use during pregnancy in patients with rheumatic conditions. Two of the 3 studies reviewed in the 2008 publication could be included in our current review. No studies were included in the review in relation to lactation. A total of 204 malformations were identified among infants exposed to NSAID, with an OR of 1.04. The number of identified cardiac defects was higher than expected, with an OR of 1.86. There seemed to be no specificity for the type of NSAID used. Among the 6 infants with orofacial clefts, 5 occurred with naproxen use and 1 with ibuprofen.

Conclusion. Only 2 studies evaluating the risk of NSAID use in patients with inflammatory arthritis were identified, with results suggesting a higher rate of cardiac malformations in infants exposed to NSAID during the first trimester. No studies evaluating the effects of other treatments, such as paracetamol, corticosteroids, muscle relaxants, neuromodulators, antidepressants, opioids, or opioid-like therapy in the specific context of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or spondyloarthritis, and no studies with respect to lactation were identified. Research is needed to improve the risk-benefit ratio of the use of pain therapies for inflammatory arthritis during pregnancy. (J Rheumatol Suppl. 2012 Sept;90:59–61; doi:3899/jrheum.120344)

Key Indexing Terms:
PAIN THERAPY INFLAMMATORY ARTHRITIS PREGNANCY LACTATION

Many autoimmune inflammatory conditions are prevalent in women during their reproductive years. Likely owing to the hyperestrogenicity, the disease activity of many inflammatory conditions may vary during pregnancy, rheumatoid arthritis having a trend towards improvement, and lupus towards exacerbation. Pain management in pregnant patients with inflammatory arthritis may therefore be a great challenge for the treating physician. Although it is essential that the disease be adequately treated, the safety of the various medications used must be closely evaluated. Our objective was to evaluate the safety of various pain medications used in pregnant or lactating patients diagnosed with one of rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), or spondyloarthritis (SpA).

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MATERIALS AND METHODS

A systematic literature review (SLR) was carried out in several steps following the updated guidelines for Cochrane systematic reviews[1]. Our review was part of the multinational 3e (Evidence, Expertise, Exchange) Initiative for generating practical recommendations about Pain Management by Pharmacotherapy in Inflammatory Arthritis[2].

Rephrasing the question. When conducting a SLR, the first step is to translate the question into an epidemiological question following the PICO method (Patients, Intervention, Comparator, Outcome)[3]. Patients were defined as women over 16 years of age either pregnant or lactating and diagnosed with one of the following inflammatory conditions: RA, PsA, AS, or SpA. Intervention was monotherapy or combination of pain therapy, including (whatever the dose, interval, or route of administration) paracetamol, nonsteroidal antiinflammatory drugs (NSAID), corticosteroids, muscle relaxants, neuromodulators, antidepressants, opioids, or opioid-like therapy. The control group included pregnant or lactating women over 16 years of age and diagnosed with one of the above 4 inflammatory conditions but not taking any of the above medications. Included outcomes were any adverse event affecting

pregnancy, mother, fetus, or baby; the passage of medication into the breast milk; and adverse effects on the lactating child. There were no trial-type limitations, with the exception of single case reports and editorials. Studies were excluded if no safety data were included, or if the studies included healthy subjects only.

Literature search. A systematic literature search was performed in Medline (1950 to May 21, 2010), Embase (January 1, 1980, to June 4, 2010) and the Cochrane Library using a comprehensive search strategy developed in collaboration with 2 experienced librarians (for details see the online Appendix available from www.3epain.com). European League Against Rheumatism (EULAR) 2008-2009 and American College of Rheumatology (ACR) 2008-2009 meeting abstracts were also searched. Review articles were also examined to identify additional studies by hand-searching reference lists. Figure 1 illustrates the results of our literature search.

Study selection. Relevant articles were selected following a systematic procedure. Titles and abstracts of all the references were screened, excluding articles that did not address the studied topic. All selected articles were then reviewed as a full report, applying the inclusion criteria defined by the PICO method. Articles that did not fulfill all inclusion criteria were excluded (see Appendix available from www.3epain.com). The level of evidence of each study was assessed according to the Oxford Centre for Evidence-based Medicine[4].

RESULTS

After removal of duplicates, a total of 3974 references and 7 meeting abstracts were identified. After title and abstract screening, 62 articles were retrieved for full-text review, of which 35 were review articles. Two articles fulfilled the inclusion criteria, the first reference being a SLR regarding the safety of NSAID use during pregnancy in women with rheumatic diseases that included a total of 3 articles[5]. The second reference was a prospective study evaluating piroxicam levels in breast milk after longterm treatment[6]. The article could not be included in our current SLR because the studied treatment, piroxicam, has been withdrawn from the market. No meeting abstracts or additional hand-search papers were included.

Impact on pregnancy. Only one study was found that fulfilled all the predefined inclusion criteria with regard to pregnancy and pain medication use. The article was a SLR published in 2008, evaluating the safety of NSAID during pregnancy in women with rheumatic diseases[5]. The SLR included 3 articles, published in 2001[7], 1996[8], and 1973[9]. The 1973 article was not included in our current SLR because the NSAID used was aspirin 3.25 g per day, a treatment regimen no longer used.

The article published in 2001[7] was a nested case-control within an observational study. This study was designed to evaluate the risk of congenital malformations with early pregnancy use of NSAID. A total of 279,734 births were identified through the Swedish Medical Birth Registry between 1995 and 1998. Of these, 72,142 women reported drug use before the first antenatal visit, and of these pregnancies, 2557 infants were exposed to NSAID in early pregnancy.

The authors then linked these pregnancies with the Swedish Register of Congenital Malformations and the Swedish Cardiology Register in order to identify cardiac malformations. Forty cases of cardiac defects associated with NSAID use were identified along with 40 other cases of NSAID use not associated with cardiac malformations. The

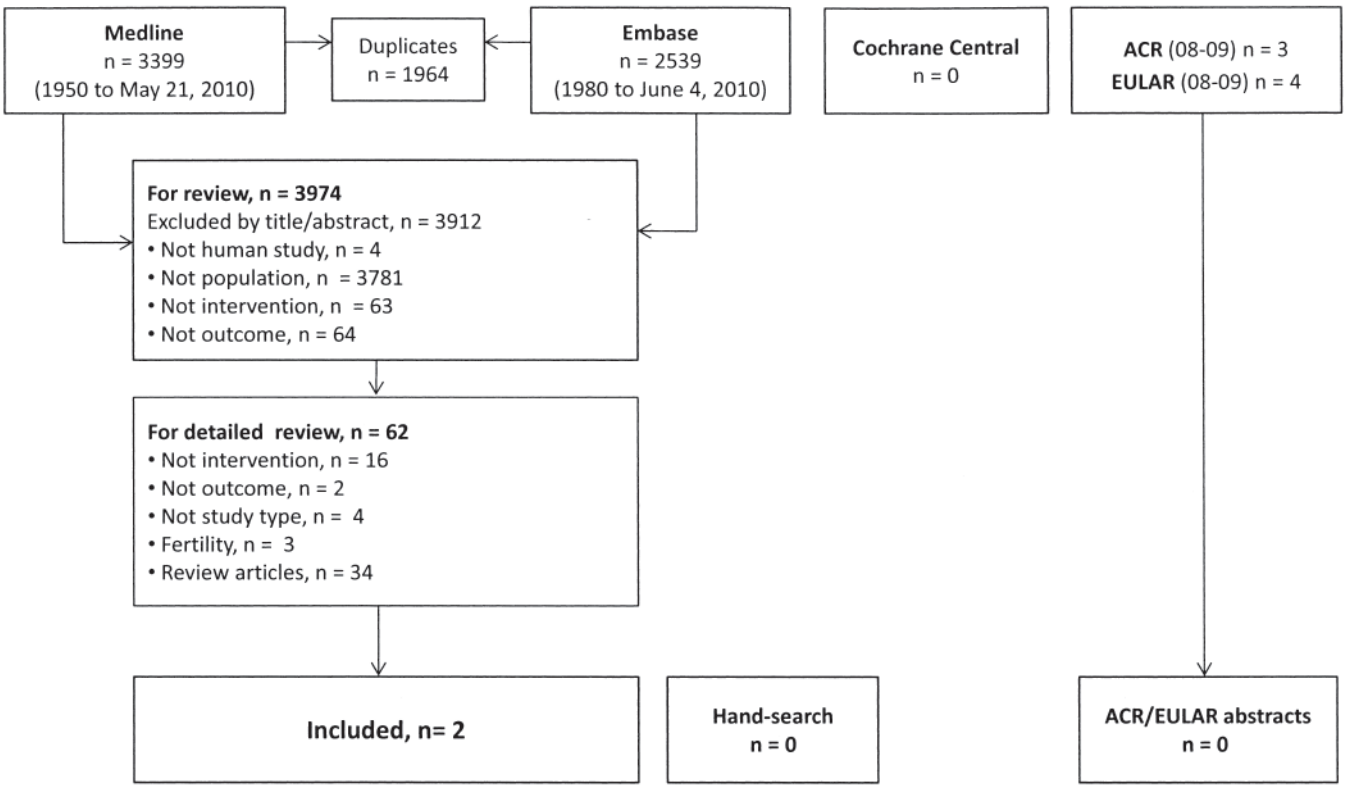

Figure 1. Literature search for articles selected for detailed review. Two articles met the inclusion criteria.

reason for NSAID use was indicated in only 14 of the 40 subjects in the outcome group and in only 21 of the 40 control subjects, and included joint problems, migraines, urinary or biliary stones, urinary tract infection, or menstrual cramps. Birth defects was the measured outcome.

A total of 104 malformations were identified among infants whose mothers used NSAID. The total malformation rate was close to the expected rate with an OR 1.04 and 95% CI 0.84–1.29 after stratification for year of birth, maternal age, parity, and smoking habits. The number of identified cardiac defects was higher than expected, with an OR of 1.86 after stratification. There seemed to be no specificity for the type of NSAID used. In total, 1129 patients were exposed to ibuprofen, with 15 cardiac defects noted (1.3%); 918 women were exposed to naproxen, with 14 cardiac defects reported (1.5%); and 574 patients were exposed to diclofenac, with 8 cardiac defects noted (1.4%). These proportions did not differ significantly. Among the 6 infants with orofacial clefts, 5 occurred with naproxen use and 1 with ibuprofen.

The article published in 1996[8] was a prospective cohort study evaluating the effect of NSAID use during pregnancy. A total of 88 patients with inflammatory rheumatic disease and with a pregnancy resulting in birth were included in the study, for a total occurrence of 94 pregnancies. Patients were divided in 2 groups: Group 1, comprising 43 patients (45 pregnancies), took no NSAID, whereas the 45 patients in Group 2 (49 pregnancies) took NSAID at some time during the pregnancy. NSAID was used throughout the pregnancy (until week 34–36) in 14 cases, whereas 35 pregnancies were exposed to NSAID for a shorter period of time, but none less than 3 weeks. The average treatment duration was 15.3 weeks (71% in the first trimester, 58% in the second trimester, and 38% in the third trimester). The reason for NSAID use was indicated for 88 of the 94, included as juvenile RA, RA, PsA, AS, reactive arthritis, and lupus. Measured outcomes included live birth, stillbirth, mode of delivery, duration of labor, birth weight, neonatal health, and birth defects.

Ninety-two live births were reported, and 2 stillbirths, for which no specifications were given other than one occurrence in each group; 14 cesarean sections were required in the treatment group versus 8 in the control group. Again, no specifications were given for this difference. There was no significant difference with respect to number of congenital malformations, length of pregnancy, length of labor, birth weight, or blood loss requiring transfusion.

Impact on nursing. Only one study was found regarding the impact on nursing and it was not included in the current SLR because the studied treatment, piroxicam, has been withdrawn from the market[6].

DISCUSSION

Our SLR summarizes and emphasizes the currently limited evidence regarding the use of various pain medications in specific inflammatory conditions such as RA, PsA, AS, and SpA. The articles retrieved through our SLR include data on NSAID only, naproxen and ibuprofen being the 2 most commonly used agents. Other than for indomethacin, there is little knowledge regarding the safety of other NSAID during pregnancy or lactation. When considering naproxen or ibuprofen in pregnancy, the fetal risk category is B when used in standard doses, such that animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. In general, there is concern in the peripartum period with respect to fetal hemorrhage, premature ductus arteriosus closure, and impaired renal function, possibly leading to decreased amniotic fluid volumes.

No studies evaluating the impact of other treatments, such as paracetamol, corticosteroids, muscle relaxants, neuromodulators, antidepressants, opioids, or opioid-like therapy in the specific context of RA, PsA, AS, or SpA were identified.

In conclusion, only 3 heterogeneous studies could be included despite the extensive literature search. We therefore cannot provide specific recommendations as to the safety of pain therapies used during pregnancy or lactation.

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