Are new agents used to treat rheumatoid arthritis safe to take during pregnancy?

Organization of Teratology Information Specialists (OTIS) study

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ABSTRACT

QUESTION I have a patient planning pregnancy who has resistant rheumatoid arthritis that will require treatment with some of the "new" medications. Which ones are safe to use during pregnancy, and which ones do we know enough about to tell whether they are safe or not?

ANSWER For most new disease-modifying biologic medications, we have few data on safety. More and more reassuring data are accumulating on azathioprine and cyclosporine. When you treat this patient, you can help in gathering such data by contacting the Organization of Teratology Information Specialists' Autoimmune Disease in Pregnancy study through Motherisk at 877 311-8972.

RÉSUMÉ

QUESTION Une de mes patientes planifie une grossesse mais elle souffre d'arthrite rhumatoïde résistante. Son problème exigera un traitement avec certains des «nouveaux» médicaments. Quels sont ceux qui sont sécuritaires à utiliser durant la grossesse et quels sont ceux qu'on connaît suffisamment pour établir leur innocuité?

RÉPONSE Nous avons peu de données sur l'innocuité de la plupart des nouveaux médicaments biologiques modificateurs de la maladie. Les données rassurantes sur l'azathioprine et la cyclosporine se font de plus en plus nombreuses. Quand vous traitez cette patiente, vous pouvez aider à recueillir de telles données en communiquant avec les responsables de l'étude des spécialistes sur les maladies auto-immunitaires durant la grossesse de l'Organization of Teratology Information par l'intermédiaire de Motherisk, au 877-311-8972.

The availability of a host of new disease-modifying antirheumatic drugs (DMARDs) has raised important questions about fetal safety for women with rheumatoid arthritis (RA) who become pregnant while they are being treated with these drugs. Because about half the pregnancies in North America are unplanned and fewer than half the women recognize they are pregnant by the fourth week of gestation, inadvertent exposure to a medication of unknown safety during a critical period in embryonic development is common. Physicians and pregnant patients are frequently faced with assessing the risk of exposure to a medication or combination of medications that has already occurred early in pregnancy, or deciding whether to continue or discontinue a medication regimen during a planned pregnancy or breastfeeding.

We summarize information on the risks of taking certain medications or classes of medications used to treat RA during pregnancy. We invite you to enrol your patients in the Organization of Teratology Information Specialists' (OTIS) studies by calling Motherisk at 877 311-8972.

Sulfasalazine

Although no controlled epidemiologic studies have been done on the prenatal effects of sulfasalazine, several large observational studies have been done on the offspring of more than 400 women with inflammatory bowel disease treated with sulfasalazine during pregnancy.[1] No indications of an association between structural defects and prenatal exposure to sulfasalazine were found. One recent case-control study that grouped sulfasalazine with other folic acid antagonist medications suggested, however, that there was about a 2- to 3-fold increased risk of neural tube defects in the offspring of women exposed to folic acid antagonist drugs early in pregnancy.[2] The numbers in that study were insufficient to calculate a risk specifically for sulfasalazine.

Leflunomide

The only peer-reviewed published data on the prenatal effects of leflunomide in humans come from a questionnaire mailed to rheumatologists regarding their prescribing practices for DMARDs.[3] In this summary with no comparison group, no malformations were reported in the offspring of 10 women who were prescribed leflunomide during pregnancy. In an ongoing prospective controlled study of RA medications in pregnancy being conducted by OTIS, 43 leflunomide-exposed women with RA were compared with 78 women with RA who did not use leflunomide and with a second group of 47

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women without RA. Preliminary data indicate rates of major birth defects were similar in all 3 groups.

Infants exposed to leflunomide were significantly more likely than infants of women without RA to be born prematurely and to be smaller. There were, however, no significant differences in these 2 measures between leflunomide-exposed infants and non-exposed infants of women with RA, suggesting that the underlying disease or other medications used to treat RA are likely associated with these adverse outcomes. Despite the minimal data on humans, the United States Food and Drug Administration has assigned leflunomide a pregnancy category X (**Table 1**). This is based on its mechanism of action (interference with synthesis of DNA and RNA) and on results of animal studies in pregnant rats and rabbits that demonstrated an increased risk of congenital malformations in their offspring (**Table 2**).

Antimalarials: chloroquine and hydroxychloroquine

Much of the literature on the prenatal effects of chloroquine relates to its use in relatively low doses (300 mg/wk) for malaria prophylaxis. No increased risk of structural abnormalities or pregnancy loss was documented following first-trimester exposure.[4] Studies on use of chloroquine and hydroxychloroquine for treatment of rheumatic diseases during pregnancy have had

Table 1. United States Food and Drug Administration categories of drugs taken during pregnancy

CATEGORY A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
CATEGORY B	Animal reproduction studies have failed to demonstrate a risk to the fetus, but there are no adequate and well-controlled studies of pregnant women.
CATEGORY C	Animal reproduction studies have shown an adverse effect on the fetus, but there are no adequate and well-controlled studies of humans. Potential benefits might warrant use of the drug for pregnant women despite potential risks.
CATEGORY D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies of humans, but potential benefits might warrant use of the drug for pregnant women despite potential risks.
CATEGORY X	Studies of animals or human beings have demonstrated fetal abnormalities or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience. The risk involved in use of the drug for pregnant women clearly outweighs the potential benefits.

Table 2. Risk associated with taking disease-modifying antirheumatic drugs during pregnancy

AGENT	PREGNANCY CATEGORY*	ADVERSE EFFECTS IN HUMAN PREGNANCY	SUMMARY RISK ASSESSMENT
Leflunomide	X	No documented increased risk of structural defects	Based on minimal data for human pregnancy, teratogenic risk is undetermined
Azathioprine	D	No documented increased risk of structural defects; effects on growth and gestational age might be related to transplant status	Although data are limited, a substantial risk of structural malformations is unlikely
Tumour necrosis factor inhibitors			
• Adalimumab	B	No documented increased risk of structural defects	Based on minimal data on human pregnancy, teratogenic risk is undetermined
• Anakinra	B	No data available on humans	Based on a lack of data on human pregnancy, teratogenic risk is undetermined
• Etanercept	B	No documented increased risk of structural defects	Based on minimal data on human pregnancy, teratogenic risk is undetermined
• Infliximab	B	No documented increased risk of structural defects	Based on minimal data on human pregnancy, teratogenic risk is undetermined
• Rituximab	C	No documented increased risk of structural defects based on a case report	Based on a lack of data on human pregnancy, teratogenic risk is undetermined

*Based on United States Food and Drug Administration categories.

controversial results, primarily because of the higher doses used to treat these disorders. As with malaria prophylaxis, however, no increased risk of congenital malformations was documented following first-trimester exposure to either of these drugs.[5,6] Studies on these drugs included more than 100 pregnant women treated with either 250 mg/d of chloroquine or 200 to 400 mg/d of hydroxychloroquine. Increased risk of spontaneous abortion and preterm delivery was noted, but both these adverse outcomes could be related to maternal underlying disease.

For adults, the main toxic effect of chloroquine and hydroxychloroquine relates to their deposition in the retina. A prospective study after exposure to these drugs during pregnancy did not reveal ocular damage in offspring.[7]

Azathioprine

Most of the data on the effects of azathioprine on fetal development have come from studies of its use to prevent transplant rejection. Reports of approximately 90 babies born to women treated with azathioprine for rheumatic diseases have been published. No increased risk of structural defects was documented in any of these studies, although sample sizes were too small to rule out any but the most dramatic risks. A recently completed large prospective, controlled study of use of azathioprine did not document increased teratogenic risk according to a personal communication from its author, M. Berkovich. As with other drugs, it is difficult to separate the possible effects of the drug from the effects of the underlying maternal disease. The increased risk of fetal death could be a consequence of azathioprine treatment for the mother's systemic lupus erythematosus.

Tumour necrosis factor inhibitors (biologics)

Little information on use of any these drugs (adalimumab, anakinra, etanercept, infliximab, rituximab) during human pregnancy has been published. Most data come from isolated case reports, retrospective surveys, and otherwise uncontrolled studies.[8-12] One case report of a woman treated with adalimumab throughout pregnancy for Crohn disease has been published. The pregnancy resulted in a normal full-term infant.

No malformations were reported in the offspring of 14 women prescribed etanercept during pregnancy and whose rheumatologists responded retrospectively to a mailed survey. Another single case report of a woman with RA and infertility who received chronic therapy with etanercept documented a normal pregnancy outcome. The abstract of an ongoing prospective controlled study of RA medications taken during pregnancy being conducted by OTIS reported on the pregnancy outcomes of 32 women exposed to etanercept and 4 women exposed to infliximab. These very small numbers showed similar rates of major birth defects in treated and control groups. Similar to findings on leflunomide in this same study, however, babies exposed to etanercept or infliximab were more likely to be born prematurely and to be smaller than infants born to mothers who did not have RA, but were similar in gestational age and birth weight to infants not exposed to these drugs whose mothers did have RA. Again, these findings suggest that maternal underlying disease or factors other than exposure to tumor necrosis factor inhibitors were involved.

Two other studies of pregnancy outcomes in women receiving infliximab have been published. The first was an analysis of 58 reports of first-trimester exposure either retrospectively or prospectively sent spontaneously to the drug manufacturer with no comparison group. Most of the women were being treated for Crohn disease. Although it is impossible from the published data to determine the exact percentage of women who had live births rather than miscarriages or elective terminations, the authors concluded that the data did not suggest an increased risk of miscarriage. Of the 5 live-born infants in this study who had complications, 2 were structurally normal but had complicated neonatal courses, and 3 had structural or developmental problems. One member of a twin pair was developmentally delayed, 1 child had tetralogy of Fallot, and 1 had intestinal malrotation. A second study, based on a retrospective chart review with no comparison group, evaluated the offspring of 10 women who received infliximab throughout pregnancy for Crohn disease. All 10 had live-born infants without structural anomalies or intrauterine growth restriction; however, 3 of the 10 babies were born prematurely.

Discussion

There are few adequately powered, well-designed studies on the safety of most medications women with RA frequently take during pregnancy. Yet, the cumulative data on sulfasalazine, azathioprine, and antimalarials are reassuring. While much less is known about the new biologic medications, they do not appear likely to pose a major teratogenic risk. Consequently, it is important for physicians to balance the potential benefits suggested by few but reassuring data with the potential risk associated with untreated moderate and severe RA. The risk-benefit ratio will vary from case to case.

One approach to meeting this challenge is that developed by OTIS, a North American network of telephone information services based in universities, hospitals, and departments of health at 18 sites throughout the United States and Canada. Members of OTIS provide risk counseling to approximately 100 000 pregnant women and health care providers each year regarding exposure to drugs during pregnancy and breastfeeding. At the same time, OTIS services collaborate to conduct pregnancy outcome studies on selected exposures.

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MOTHERISK

Motherisk questions are prepared by the **Motherisk Team** at the Hospital for Sick Children in Toronto, Ont. **Dr Chambers, Dr Tutuncu, Ms Johnson**, and **Dr Jones** are members of the California Terratogen Information Service and **Dr Koren** is Director of the Motherisk Program. **Dr Koren** is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation and, in part, by a grant from the Canadian Institutes of Health Research. He holds the Ivey Chair in Molecular Toxicology at the University of Western Ontario in London.

Do you have questions about the effects of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the **Motherisk Program** by fax at 416 813-7562; they will be addressed in future Motherisk Updates.

Published Motherisk Updates are available on the College of Family Physicians of Canada website (**www.cfpc.ca**) and also on the Motherisk website (**www.motherisk.org**).

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