Review

Human pregnancy safety for agents used to treat rheumatoid arthritis: adequacy of available information and strategies for developing post-marketing data

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Abstract

For female patients with rheumatoid arthritis, the availability of a host of new disease modifying antirheumatic drugs has raised important questions about fetal safety if a woman becomes pregnant while she is being treated. In addition, there is limited safety information regarding many of the older medications commonly used to treat rheumatoid arthritis in women of reproductive age. Current summary pregnancy risk information for selected medications used to treat rheumatoid arthritis is reviewed in the context of the pregnancy label category. In addition, the strengths and weaknesses of post-marketing strategies for developing new pregnancy safety information are described.

Introduction

For female patients with rheumatoid arthritis (RA), the availability of a host of new disease modifying antirheumatic drugs (DMARDs) has raised important questions about fetal safety if a woman becomes pregnant while she is being treated. In addition, there is limited safety information regarding many of the older medications commonly used to treat RA in women of reproductive age.

Although pre-marketing clinical trials and post-marketing safety studies can address questions regarding safety in most segments of the population, pregnant women constitute one special group for whom ethical concerns prohibit the establishment of human drug safety information as part of the drug development and approval process. However, once a new drug is marketed or an existing drug is used for a new indication, if women of reproductive age are prescribed the drug, pregnancy exposures will inevitably occur. This is due to the fact that about half of pregnancies in the US are unplanned [1], and overall fewer than 50% of women recognize they are pregnant by the fourth week in gestation [2], leading to the common occurrence of inadvertent exposure to a medication of unknown safety during a critical period in embryonic development.

Thus, the rheumatologist and the pregnant patient are frequently faced with the dilemma of assessing the potential risk of an exposure to a medication or combination of medications that has already occurred early in pregnancy, or of making the decision to continue or discontinue a medication regimen during a planned pregnancy or breastfeeding.

In the US, the resource that clinicians and patients rely on most heavily in evaluating individual risk is the US Food and Drug Administration's (FDA) Pregnancy Category: A, B, C, D, X [3]. Pregnancy safety cannot be ethically evaluated in pre-marketing human clinical trials. In the post-marketing setting, isolated case reports of adverse pregnancy outcomes are difficult to interpret without a known denominator of exposed women, and post-marketing controlled observational studies are not systematically conducted. Therefore, there are insufficient human pregnancy safety data available for more than 80% of drugs currently available on the US market [4].

Thus, as shown in Table 1, the pregnancy category is a designation that is almost exclusively derived from preclinical animal reproductive and developmental toxicity studies. This is despite the fact that animal studies are not always predictive of human pregnancy risk. Drugs that have been identified as teratogenic in selected animal species may have been tested at doses that far exceed the normal human therapeutic range. Furthermore, even at comparable doses, medications shown to be teratogenic in one or more animal

COX = cyclooxygenase; DMARD = disease modifying antirheumatic drug; FDA = US Food and Drug Administration; NSAID = non-steroidal anti-inflammatory drug; OTIS = Organization of Teratology Information Specialists; RA = rheumatoid arthritis.

Table 1

FDA pregnancy categories

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

species may not produce the same results in humans or any adverse effects at all. Conversely, drugs that have demonstrated no adverse effects in selected animal species may in fact be human teratogens [5]. Therefore, until adequate human pregnancy safety data are available, the pregnancy category designation has limited value in predicting safety or risk.

The purpose of this paper is two-fold. First, we present current summary pregnancy risk information for selected medications or classes of medications used to treat RA. This information is intended to describe both the substantial gaps in current knowledge as well as the frequent discordance between the FDA Pregnancy Category and currently available data. Secondly, we compare the strengths and weaknesses of post-marketing strategies for developing new pregnancy safety information, with a specific focus on pregnancy registries using the Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in Pregnancy Project design for illustration.

Review of pregnancy safety information

A brief review of the literature and pregnancy exposure risk assessment for selected agents used to treat RA is presented below. In addition, in Tables 2 through 4, a summary risk statement in comparison with the FDA Pregnancy Category is listed for each agent or selected agents within a class.

Anti-inflammatory agents

Corticosteroids

An association between prenatal exposure to corticosteroids, such as prednisone, and intrauterine growth restriction in humans has long been recognized. The risk appears to be dose related, suggesting that this concern can be minimized with lower doses [6-8]. Although cortisone is known to cause cleft palate in rats and mice, until recently no such association has been suspected in humans [9]. However, among four recent case-control studies and a meta-analysis, three studies and the meta-analysis conclude that systemic corticosteroid use in the period surrounding the time of conception appears to be associated with a three- to six-fold increased risk for cleft lip with or without cleft palate and possibly cleft palate alone. It is unclear to what extent this association is explained by the various underlying maternal diseases involved in these studies or other unmeasured confounders [10-14]. To put these relative risks into perspective, in that the population birth prevalence of all oral clefts combined is approximately 1 per 1,000 live births, systemic corticosteroid use is associated with a risk of either cleft lip with or without cleft palate or cleft palate alone of approximately 1.3 to 3.3 for every 1,000 pregnancies exposed during the critical period for lip/palate closure. Based on these data, it is suggested that the risk associated with prenatal exposure to these medications is minimal.

Non-steroidal anti-inflammatory drugs

The non-steroidal anti-inflammatory drugs (NSAIDs) include celecoxib, indomethacin, ibuprofen, sulindac, ketoprofen, diclofenac, meloxicam, ketorolac, naproxen, nimesulide and piroxicam.

A number of studies in which pregnancy outcome has been documented in the offspring of women treated during early pregnancy with various NSAIDs have been published [15-24]. Based on those studies, in general it is not thought that NSAIDs are serious teratogens but may be associated with low risks for certain congenital malformations and possibly miscarriage.

Three case-control studies have examined the association between ibuprofen and gastroschisis, a rare defect that occurs normally in about 1 in 10,000 live births. These studies have produced conflicting results. One study demonstrated a four-fold increased risk when mothers reported

Table 2

Anti-inflammatory medications

Class	Agent	FDA pregnancy category	Adverse effects in human pregnancy	Summary risk assessment
Corticosteroids	Prednisone Cortisone All others	C D C	Oral clefts increased risk (two- to three-fold). Intrauterine growth restriction (dose related)	Based on available data, teratogenic risk for corticosteroids is minimal
NSAIDs	Celecoxib Diclofenac Ketorolac Prixicam All others	C C C C B	Ibuprofen associated with increased risk (two- to three-fold) for gastroschisis. NSAIDs associated with increased risk for spontaneous abortion; possible increased risk for cardiac defects; premature closure of the ductus arteriosus with third trimester use	Significant risk for premature closure of the ductus arteriosus and other complications when exposure occurs in late pregnancy; minimal or undetermined risk for structural defects following first trimester exposure
	All NSAIDs in third trimester	D		

NSAIDs, non-steroidal anti-inflammatory drugs.

Table 3

Disease-modifying antirheumatic drugs

Agent	FDA pregnancy category	Adverse effects in human pregnancy	Summary risk assessment
Methotrexate	X	Pattern of malformation, including apparent dose-related abnormalities of growth, craniofacies, limb development, and neurodevelopment	Based on available data, contraindicated in human pregnancy; unknown magnitude of risk
Sulfasalazine	B	Possible increased risk for malformations suggested in two studies; other studies negative	Based on limited data, a substantial teratogenic risk is unlikely
Leflunomide	X	No documented increased risk for structural defects in humans	Based on minimal data in human pregnancy, teratogenic risk is undetermined
Hydroxychloroquine	C	No documented increased risks for malformations; theoretical concerns for retinal toxicity and ototoxicity, but no reported cases	Although data are insufficient, a substantial teratogenic risk is unlikely
Azathioprine	D	No documented increased risk for structural defects; growth and gestational age effects may be related to transplant status	Although data are limited, a substantial risk for structural malformations is unlikely
Cyclosporine	C	No documented increased risk for structural defects; growth and gestational age effects may be related to transplant status	Based on limited data, risk for structural malformations is unlikely
Chlorambucil	D	Case reports only - two with unilateral renal agenesis	Based on insufficient data, teratogenic risk is undetermined
Cyclophosphamide	D	Pattern of malformation including increased risk for abnormalities of growth, craniofacies, limb development, and neurodevelopment	Based on available data, contraindicated in human pregnancy; unknown magnitude of risk

using ibuprofen in the three month period around the time of conception, while the other two studies showed no such association [19-21]. It is important to recognize that although one study has raised the possibility of increased risk, gastroschisis is so uncommon that the potential absolute risk is extremely low. In addition, one large Swedish cohort study has shown an approximate two-fold increased risk for cardiac defects with any NSAID use in early pregnancy and an approximate three-fold increased risk for oral clefts with early pregnancy use of NSAIDs, specifically naproxen [16]. A second case-control study using the same data source also showed an approximately two-fold increased risk for cardiac defects in association with early pregnancy use of naproxen [22]. In contrast, in a Danish study of NSAID use in early pregnancy, no increased risk for malformations, preterm delivery or low birth weight was noted [23]. However, this

Table 4

Disease modifying anti-rheumatic drugs: biologics

Agent	FDA pregnancy category	Adverse effects in human pregnancy	Summary risk assessment
Etanercept Infliximab Adalimumab	B B B	No documented increased risk for structural defects	Based on minimal data in human pregnancy, teratogenic risk is undetermined
Rituximab	C	No documented increased risk for structural defects based on case report	Based on lack of data in human pregnancy, teratogenic risk is undetermined
Anakinra	B	No available human data	Based on lack of data in human pregnancy, teratogenic risk is undetermined

study and one additional US study have both shown an increased risk for spontaneous abortion (two- to seven-fold) when NSAIDs are used early in pregnancy [23,24]. At present, these data do not provide sufficient or conclusive evidence that early pregnancy use of any NSAID, including naproxen, causes heart defects or oral clefts, even at a low level of risk. Two studies show an increased risk for spontaneous abortion, although it is unclear to what extent the indication for use of the medication may have contributed to pregnancy loss.

Despite the demonstrated lack of substantial teratogenic risk following first trimester exposure to NSAIDs, a number of risks have been documented when fetal exposure occurs late in pregnancy. Premature closure of the fetal ductus arteriosus with resultant pulmonary hypertension has been noted in association with third trimester use of NSAIDs [25]. Renal dysgenesis leading to oligohydramnios has been reported following later pregnancy exposure to indomethacin, ibuprofen, naproxen, ketoprofen, nimesulide, and piroxicam [26]. Necrotizing enterocolitis and ileal perforation as well as intraventricular hemorrhage and cystic brain lesions have been seen in preterm infants exposed to indomethacin prior to delivery [27,28]. These complications are thought to be related to the extent to which the individual NSAID selectively inhibits cyclooxygenase (COX)1 as opposed to COX2. Based on studies in rats and rabbits, compounds that selectively inhibit COX1 or have a high ratio of COX1/COX2 inhibition are more likely to be associated with the induction of developmental defects [29].

The extent of the ductal constriction, and possibly the other neonatal complications listed above, are gestational-age dependent. Although *in utero* ductal constriction seldom occurs with prenatal exposure earlier than 27 weeks' gestation, a significant risk is present at or beyond 32 weeks' gestation, leading to the recommendation that NSAIDs be discontinued prior to that gestational age. In cases in which that approach is followed, neonatal complications in full term babies are rare.

Disease modifying antirheumatic drugs

Methotrexate

Both aminopterin and its methyl derivative, methotrexate, have been associated with a specific pattern of malformation in infants born to mothers who use one of these medications early in pregnancy. The principal features of this pattern, referred to as the aminopterin/methotrexate syndrome, include prenatal onset growth deficiency, severe lack of calvarial ossification, hypoplastic supraorbital ridges, small low set ears, micrognathia, limb abnormalities, and in some cases developmental delay [30-31]. The majority of affected infants have been born to women treated with high dose methotrexate for psoriasis, neoplastic disease and/or as an abortafacient [32].

Pregnancy outcomes in 23 women with RA who had 25 pregnancies treated with methotrexate have been reported [32-35]. The dosage of methotrexate in these pregnancies was low, ranging from 7.5 to 12.5 mg/week. Nine of the 25 pregnancies resulted in spontaneous abortions and 14 resulted in normal babies. One woman who received a total methotrexate dose of about 100 mg over the first 8 weeks of her pregnancy had a baby with the aminopterin/methotrexate syndrome, and two women electively terminated their pregnancies. In another case series, pregnancy outcome was reported for 28 women, 22 of whom were treated for RA, and all but one whose doses were <15 mg/week during early pregnancy. Five pregnancies ended in elective termination, four in spontaneous abortion and the remaining 19 resulted in live births. One child presented with mild neonatal abnormalities consisting of bilateral metatarsus varus and right eyelid angioma [36]. Based on these cases, it has been suggested that the maternal methotrexate dose necessary to produce the aminopterin/methotrexate syndrome is greater than 10 mg/week [32]. Furthermore, it has been suggested that the critical period of exposure relative to the risk for the syndrome is between six and eight weeks post-conception [32]. However, data are still insufficient to verify the exact threshold dose, the critical window of exposure, or the magnitude of the risk for the syndrome following first trimester exposure to methotrexate.

The concomitant use of folic acid supplements to protect against the deleterious effects of prenatal methotrexate exposure has not been evaluated. However, a recent study suggests that the folic acid component of multivitamins may reduce the risk of neural tube defects, oral clefts, cardiovascular defects, and urinary tract defects in the offspring of women taking other folic acid antagonists including trimethoprim, triamterine and sulfasalazine [37].

Sulfasalazine

Three observational studies have been conducted including the offspring of more than 300 women with inflammatory bowel disease treated with sulfasalazine during pregnancy [38-40]. No indication of an association between structural defects and prenatal exposure to sulfasalazine is evident based on those studies. However, in two recent case-control studies, both using the same dataset, an approximate two- to three-fold increased risk for neural tube defects, cardiovascular defects and oral clefts was documented following early pregnancy exposure to one of a group of folic acid antagonist medications. Sulfasalazine was one of the medications classified in this group [37,41]. Of particular significance, the adverse effects of this group of medications were diminished by the use of multivitamin supplements containing folic acid. Numbers of exposed women were insufficient in either of these studies to calculate a risk specifically for sulfasalazine [37,41]. In another study, which was survey based, an overall increased risk for congenital anomalies with prenatal sulfasalazine exposure was suggested [42]. However, another population-based case control study found no such association [43]. Published case reports have documented five children with structural defects born to four women treated during pregnancy with sulfasalazine. These include two children with a ventricular septal defect and aortic coarctation [44,45], one child with cleft lip/palate and hydrocephalus [45], and a stillborn twin pair, one with left-sided renal agenesis and a rudimentary left uterine cornu and the other with bilateral renal agenesis [46].

Although no large well-controlled studies of sulfasalazine used for the treatment of RA have been published, based on the available data, even if there is a risk associated with sulfasalazine, it is likely to be very low. However, because of the potential risk associated with folic acid antagonist medications, when sulfasalazine is prescribed to a women of childbearing potential, the routine recommendation to take folic acid containing vitamin supplements is especially important.

Leflunomide

The largest series of peer-reviewed published data available regarding the prenatal effects of leflunomide in humans is from a questionnaire mailed to rheumatologists regarding their practices when prescribing DMARDs [47]. In this summary of retrospectively reported pregnancies with no comparison group, there were no malformations reported among the offspring of 10 women who were prescribed leflunomide during pregnancy. An additional three case reports of women with first trimester exposure to leflunomide were reported by an Italian Teratology Information Service. Two of these pregnancies ended in voluntary termination and the third in a normal live birth [48]. Another 43 pregnancy outcomes with first-trimester exposure to leflunomide have been published in abstract [49]. In an ongoing prospective controlled study of RA medications in pregnancy being conducted by the North American Organization of Teratology Information Specialists, 43 leflunomide-exposed women were compared to 78 women with RA who did not use leflunomide and a second group of 47 women without RA. Based on very small numbers, rates of major birth defects were similar between the groups. Infants exposed to leflunomide were significantly more likely than non-diseased comparison infants to be born prematurely and were significantly smaller in birth weight. However, there were no significant differences on these two measures between the leflunomide-exposed group and the RA comparison group, suggesting that the underlying disease and/or other medications used to treat RA are likely related to these adverse outcomes.

Despite the minimal data in humans, leflunomide has been assigned an FDA pregnancy category X. This is based on its mechanism of action (interference with DNA and RNA synthesis) [50], as well as animal studies in pregnant rats and rabbits that demonstrated an increased risk for congenital malformations in their offspring [51]. However, based on a lack of adequate data in human pregnancy, at the present time, the teratogenic risk of leflunomide is unknown.

Hydroxychloroquine

Much of the literature regarding antimalarials is based on the prenatal effects of the drug chloroquine used in relatively low doses (300 mg/week) for malaria prophylaxis [52-54]. In these studies, no increased risk for structural abnormalities or pregnancy loss was documented following first trimester exposure. Relative to the use of antimalarial drugs for the treatment of rheumatic diseases, additional studies have been required because of the higher doses used for treatment of those disorders. However, no increased risk for congenital malformations has been documented following first trimester exposure to hydroxychloroquine for the treatment of connective tissue disorders in several small studies [55-57]. Furthermore, in a controlled study of 133 women with connective tissue disorder, no increased incidence of adverse pregnancy outcomes was noted [58]. Increased risks for spontaneous abortion and preterm delivery have been reported in studies of chloroquine and hydroxychloroquine used primarily for the treatment of lupus, but both of these adverse outcomes may be related to the maternal underlying disease [59-62].

Based upon the retinal toxicity and ototoxicity of chloroquine both in animals and humans [63,64], theoretical concerns for these effects with hydroxychloroquine have been raised.

However, to date no case reports of hearing or vision impairment associated with prenatal hydroxychloroquine have appeared in the literature, and in the limited number of children who have been systematically evaluated, opthalmalogical examinations have been normal [55,58]

In summary, the prenatal effects of high dose hydroxychloroquine used for the treatment of RA have not been studied adequately. However, the available data on the use of hydroxychloroquine for other rheumatic diseases is not suggestive of an increased risk.

Azathioprine

Most of the data on the effects of azathioprine on fetal development have come from studies of its use for prevention of transplant rejection [65-69]. However, reports of approximately 190 babies born to women treated with azathioprine for inflammatory bowel disease or lupus have been published [70-74]. No increased risk for structural defects has been documented in any of these studies, although sample sizes are only sufficient to rule out large risks for any specific major birth defect. An increased frequency of prematurity and intrauterine growth restriction following prenatal exposure to azathioprine has been noted in the offspring of women with renal transplants; however, it is possible that the mother's transplant status itself is a contributory factor [65-69]. Similarly, it is difficult to separate the possible effects of the drug from the underlying maternal disease in attributing the increased risk for fetal death noted in one study in association with maternal azathioprine treatment for systemic lupus erythythematosus [71].

Cyclosporine

A substantial amount of data regarding the prenatal effects of cyclosporine, used in combination with other drugs for the prevention of transplant rejection, has been published [75-78]. An increased risk for structural defects has not been documented in these studies. Of the 16 children who had defects, no consistent pattern of malformations was documented. The increased incidence of prematurity and intrauterine growth restriction that has been consistently noted in these studies is possibly attributable to the maternal transplant status. Furthermore, a meta-analysis of studies evaluating outcomes for a combined sample of 410 pregnancies with prenatal exposure to cyclosporine did not produce statistically significantly increased risks for major malformations, preterm delivery or low birth weight relative to controls [79]. Recognized toxicities of cyclosporine include nephrotoxicity and hypertension. Recent animal studies have suggested that prenatal exposure to cyclosporine was associated with long-term systemic and renal effects that were not noted in the newborn period [80]. At the present time, it is suggested that a substantial risk for malformations following prenatal exposure to cyclosporine is unlikely. However, long-term effects in humans prenatally exposed to this drug require further evaluation [81].

Other agents: chlorambucil and cyclophosphamide

Although rarely used in the treatment of RA, pregnancy outcome has been reported in four women treated with chlorambucil. Unilateral renal agenesis was reported in two of the four [82-83]. No epidemiological study regarding human pregnancy outcome has been published, although these findings are consistent with the animal data [84]. These data are insufficient to substantiate teratogenic risk; however, if such a risk exists, the magnitude of the risk in humans is unknown.

Similarly, cyclophosphamide is uncommonly used in the treatment of RA, except in patients who have systemic lupus erythromatosus. Eight case reports documenting a unique pattern of malformation in infants prenatally exposed to cyclophosphamide have been published [85]. The principle features of this disorder, referred to as the cyclophosphamide embryopathy, are similar to those seen following prenatal exposure to methotrexate and include growth deficiency, craniofacial anomalies, and absent fingers and toes. Among the three case reports in which infants survived and for which developmental information was available, significant delays were noted in all. An additional five case reports of cyclophosphamide use to treat lupus have been reported in the literature. Two pregnancies with first-trimester exposure ended in spontaneous abortion, two with second trimester exposure ended in fetal demise, and one with treatment initiated in the second trimester ended with a normal live born infant [86,87]. Although no epidemiological studies of prenatal exposure to cyclophosphamide have been published, the similar pattern of malformation seen in case reports suggests that cyclophosphamide is a human teratogen, although the magnitude of risk is unknown.

Tumor necrosis factor inhibitors: biologics etanercept, infliximab, adalimumab

Minimal human pregnancy information has been published for any of these medications, and the majority of data consists of isolated case reports, retrospective surveys and otherwise uncontrolled studies.

No malformations were reported in the offspring of 14 women who were prescribed etanercept during pregnancy and whose rheumatologists responded retrospectively to a mailed survey [47]. Another single case report of normal pregnancy outcome in a woman with RA and infertility who received chronic therapy with etanercept has been reported in the literature [88]. From an ongoing prospective controlled study of RA medications in pregnancy being conducted by the North American Organization of Teratology Information Specialists, 32 pregnancy outcomes following etanercept exposure and 4 following infliximab exposure have been reported in abstract. Based on very small numbers, there was no excess of major birth defects in comparison to the two control groups. However, similar to the findings with leflunomide from this same study, etanercept or infliximab-exposed infants were more likely to be born prematurely and

to be lower in birth weight than infants whose mothers did not have RA, but were similar in gestational age and birth weight to unexposed infants whose mothers did have RA. These preliminary findings suggest that the maternal underlying disease or factors other than exposure to tumor necrosis factor inhibitors were involved [89].

Two other studies involving pregnancy outcome in women receiving infliximab have been published. The first of these involves analysis of 58 spontaneous reports of 1st trimester exposed pregnancies either retrospectively or prospectively reported to the drug manufacturer with no comparison group [90]. The majority of women were being treated for Crohn's disease. Although it is not possible from the published data to determine the exact percentage of women who had live births as opposed to spontaneous abortions or elective terminations, the authors conclude that the data did not suggest an increased risk for pregnancy loss. Of the five live born infants in this series who had complications, two were structurally normal but had complicated neonatal courses and three had structural or developmental problems. One member of a twin pair was developmentally delayed, one child had Tetralogy of Fallot and one had intestinal malrotation. In a second study based on a retrospective chart review with no comparison group, the offspring of 10 women who received infliximab treatment throughout pregnancy for Crohn's disease were evaluated [91]. All 10 were live born infants without structural anomalies or intrauterine growth restriction; however, 3 of the 10 were born prematurely.

One case report of a woman treated with adalimumab throughout pregnancy for Crohn's disease has been published, and this pregnancy resulted in a normal full-term infant [92].

One additional abstract summarized the results of an on-line survey of rheumatologists. Of 463 pregnancies identified by rheumatologists, detailed data were gathered on 95 pregnancies, 84 of which were determined to have been exposed to a tumor necrosis factor inhibitor. Of those cases, 81% were exposed to etanercept, 12% to infliximab, and 9% to adalimumab [93]. Outcomes as reported by rheumatologists for the entire group of exposed women were similar to expected rates in the general population, although there was no formal control group. At present there is insufficient information to draw conclusions about the safety of these medications during human pregnancy, but the available data have not raised concerns.

Other biologics: rituximab and anakinra

Two case reports have been published describing women with non-Hodgkins lymphoma who were treated with rituximab and both of whom were reported to have normal babies [94,95]. To date no published information is available on the use of anakinra in pregnancy. Therefore, information is insufficient to evaluate the safety of these medications in pregnancy.

Discussion

As indicated by this review, there is a general lack of adequately powered and well-designed studies regarding pregnancy safety for the majority of medications frequently used by women with RA during pregnancy. Furthermore, as highlighted in Tables 2 through 4, there are apparent inconsistencies between the FDA Pregnancy Category and the risk assessment reflective of the human data for a number of these medications. For example, although there is extremely sparse or no human data for all six of the newer DMARDs, including leflunomide and the new biologics, pregnancy categories for medications in this group include B, C and X. Similarly, for azathioprine, chlorambucil and cyclophosphamide, the teratogenic risk based on the available human data ranges from 'unlikely', 'undetermined' to 'contraindicated' during pregnancy, and yet all three of these medications carry an FDA Pregnancy Category D. These discrepancies are critically important for the rheumatologist and the pregnant patient as the FDA category is frequently relied upon as the primary determinant of whether or not a medication is safe to use in pregnancy.

In addition to the lack of sufficient quantity of human data for most medications, the quality of human data that is available is limited. Retrospective adverse event or case reports lack denominator information and cannot demonstrate an excess risk over baseline; survey data often suffer from poor response rates, which can threaten the validity of conclusions; uncontrolled studies with no attention to potential confounding, including confounding by maternal disease, are difficult to interpret; and information on outcomes is often incomplete without comprehensive data on the range of outcomes, including malformations, fetal growth and preterm delivery.

Yet, the demand for this information is urgent, particularly when a new drug is marketed and likely to be used by women of reproductive age. As a result, pregnancy registries have become increasingly utilized as a post-marketing tool for collecting pregnancy safety information as quickly as possible for a new drug or for a previously marketed drug that is being used for a new indication.

The common elements of 'traditional' pregnancy registry designs include enrollment on the basis of a pregnancy exposure to a specific target medication, collection of pregnancy exposure and outcome information (either retrospectively or prospectively, most commonly collected from health care providers, and outcomes usually restricted to major birth defects), and comparison of those outcomes to expected numbers (usually general population rates for major birth defects).

The 'traditional' design of pregnancy registries has led to a number of epidemiological concerns about the validity of conclusions that can be drawn from such studies. In

response to this, in 2002 the FDA Center for Drug Evaluation and Research (CDER) published guidelines for the conduct of pregnancy registries aimed at setting uniform standards for these kinds of observational studies [96]. As specified in that document, issues related to study validity include prospective recruitment of a sufficient sample size of exposed pregnant women (i.e., while still pregnant and before prenatal diagnosis), adequate detail and accuracy in exposure and outcome information, an appropriate comparison group, and minimal lost-to-follow-up.

Each of these issues presents significant challenges in the real world. One approach to meeting these challenges 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 US and Canada. OTIS member services provide risk counseling to approximately 100,000 pregnant women and health care providers per year regarding pregnancy and breastfeeding exposures. At the same time, OTIS services collaborate to conduct pregnancy outcome studies for selected exposures [97]. One such study is the OTIS Autoimmune Diseases in Pregnancy Project, first initiated in its present form in 2004 [98].

This project represents a new effort involving the collaboration of OTIS member services, rheumatologists, pharmaceutical company sponsors, and pregnant women who are interested in contributing to better knowledge about the safety of medications used to treat RA. A prospective cohort study design is used with women recruited on the basis of having a diagnosis of RA, regardless of the medications used to treat the disease. In addition, pregnant women are recruited who do not have RA but have contacted an OTIS member service with questions about other exposures not deemed to be teratogenic. Recruitment is accomplished through referrals of spontaneous callers to OTIS member services, direct referrals through rheumatologists and other health care providers, and self-referral of women through the internet or other promotional methods.

Unique features of the OTIS study design include the following. First, the study objectives are not limited to evaluation of the safety of a single drug but rather to the evaluation of the wide variety of medications that are used to treat a specific disease during pregnancy. Second, the objectives of the study are not limited to estimation of the risk of major birth defects, but rather include a more comprehensive evaluation of the spectrum of adverse pregnancy outcomes, including spontaneous abortion, reduced birth size, preterm delivery, and postnatal growth deficiency. Third, the evaluation of each infant for birth defects is performed by one of a team of specialists who use a standard checklist to examine each child for any structural abnormalities, including both major and minor birth defects. Fourth, rather than comparing outcomes to a national population standard, the OTIS study employs disease-matched and non-diseased comparison groups recruited through the same referral mechanisms used to recruit exposed women. This allows for more appropriate comparisons regarding medications used specifically to treat RA, while at the same time controlling for the underlying disease and disease severity. Fifth, a commitment to completion of the study is made by the pregnant woman herself, so that complete outcome information is typically collected on 95% or more of all subjects. And sixth, enrollment of the pregnant woman herself allows for repeated and comprehensive collection of pregnancy exposure timing and dose information, including over-the-counter drugs, and information on potential confounding variables such as alcohol and tobacco use. This type of detailed information is usually not reliably available from secondary sources such as medical records or health care provider reports.

In addition, the OTIS Autoimmune Diseases in Pregnancy Project offers an immediate benefit to research participants as the OTIS project staff are available to provide individual counseling regarding any and all exposures that may have occurred during pregnancy.

Conclusion

The availability of several new medications available to the rheumatologist for the treatment of patients with RA has dramatically changed the short and long-term prognosis for these patients. However, at the same time, little is known about the prenatal effects of these medications. In addition, despite the length of time many of the older drugs have been marketed, limited data are available regarding their reproductive or developmental toxicity, particularly when used for the treatment of RA. Although the FDA pregnancy categories have provided some guidance for rheumatologists treating pregnant women as well as women in their reproductive years, the lack of knowledge about the effects of these drugs in human pregnancy makes these categories ineffective when counseling women regarding their reproductive risks. Through increasing awareness, it is hoped issues relating to reproductive toxicity will become a critical component of our public health agenda.

Competing interests

CDC and KLJ receive research funding from Amgen, Abbott Laboratories, Sanofi-Aventis, Teva Pharmaceuticals, Sandoz, Barr Laboratories, Apotex, and Kali Laboratories.

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