

Management of RA medications in pregnant patients

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Abstract | A desire for children or the presence of pregnancy limits the drug therapy options for a woman with rheumatoid arthritis. Combination therapies that include methotrexate or new drugs that have not been studied or used in pregnant patients must be excluded, even though they might be highly efficacious. With few exceptions, the reason for this exclusion is not the proven teratogenicity of the drugs, but the absence of proven safety for the fetus. Whereas methotrexate, leflunomide, abatacept and rituximab must be withdrawn before a planned pregnancy, tumor necrosis factor inhibitors and bisphosphonates can be continued until conception. Antimalarial agents, sulfasalazine, azathioprine and ciclosporin are compatible with pregnancy, and so can be administered until birth. Corticosteroids and analgesics such as paracetamol (acetaminophen) can also be used throughout pregnancy. NSAIDs can be safely administered until gestational week 32. The most important consideration when managing rheumatoid arthritis medications during pregnancy is that therapy must be tailored for the individual patient according to disease activity.

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the effects of methotrexate on the fetus.
- 2 Identify the disease-modifying antirheumatic drugs (DMARDs) that should be discontinued prior to conception.
- 3 List the DMARDs that may be continued during gestation.
- 4 Describe the treatment of rheumatoid arthritis flares during pregnancy.

Introduction

Rheumatoid arthritis (RA) affects twice as many women as men, and the incidence of the disease in both sexes steadily increases between the ages of 18 and 85 years.¹ As women

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in affluent, Western countries frequently postpone their first pregnancy until the fourth decade of life, the proportion of RA patients becoming pregnant after disease onset will increase. In women with RA who plan to become pregnant, a therapeutic regimen is required that quickly induces remission or maintains improvements already achieved, and that is at the same time compatible with pregnancy. These requirements exclude several highly efficient immunosuppressive and biologic drugs and reduce the range of combination therapies. Retrospective and small prospective studies have reported improvements of disease activity in 70–90% of pregnant patients with RA. Subsequently, however, two large prospective studies that used validated measurements of disease activity found improvements during pregnancy in only 63% and 48% of patients, respectively.^{2–3} Complete remission was reported in less than 20% of patients.² Consequently, some form of drug treatment will be necessary for 40–50% of pregnant RA patients. This Review evaluates the therapy of RA with regard to the compatibility of various medications with pregnancy. Recommendations in this Review are based on a 2006 consensus paper from 29 international experts in the fields of internal medicine, rheumatology, obstetrics, pediatrics, and genetics.⁴ These recommendations have been updated according to new data where appropriate. It should be recognized that management strategies and recommendations for prescribing antirheumatic medications during pregnancy may differ by region depending on guidelines published by national specialist associations.

Planning a pregnancy

In regard to patients with RA who plan to become pregnant, the treating physician can be presented with two scenarios: the patient with early RA in need of effective

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control of progressive, erosive disease, or the patient with established disease. The latter might be in remission and on stable medication, or might present with active disease that requires adjustments to therapy. The question for the clinician is which monotherapies or combination therapies are suitable for use during early pregnancy, and which must be prophylactically withdrawn before a planned pregnancy? Combinations of immunosuppressive and biologic agents are among the most effective therapies for RA. However, most combinations include methotrexate—a potential teratogen—or drugs for which the data are insufficient to claim safety during pregnancy. As discussed in more detail below, certain drugs should be withdrawn before the patient becomes pregnant (Table 1). The aim of therapy in a patient with RA who desires children is to induce remission or substantial improvement in disease activity by use of the most effective therapy available. As soon as stable improvement is achieved, therapy should be changed to include only drugs compatible with pregnancy (Figure 1).

Drugs incompatible with pregnancy

Methotrexate

Methotrexate exposure in the first trimester increases the risk for congenital abnormalities of the central nervous system, cranial ossification, the limbs and the palate, and can cause growth retardation in animals and humans.⁵ Methotrexate is a methyl derivative of the folate antagonist aminopterin. Active metabolites of methotrexate remain in cells or tissues for several months after cessation of therapy.⁵ The most vulnerable time for embryotoxicity has been suggested to be between 5 and 8 weeks of gestation.⁶ However, fetal malformations have also been observed before 5 weeks and after 11 weeks.⁷

In the rheumatology literature, first-trimester exposure to once-weekly methotrexate doses of ≤ 20 mg has been reported for 101 pregnancies.^{8–11} Induced abortions were performed in 18 cases, and 20 miscarriages occurred. Among the pregnancies that proceeded to term, five children had congenital anomalies, including one child with the multiple skeletal abnormalities typical of the aminopterin syndrome.¹² Birth weights of the full-term infants were within the normal range. For low-dose, once-weekly methotrexate therapy in patients with rheumatic disease, the risk for congenital anomalies after first-trimester exposure is in the range of 5–10%. No definite dosage threshold for fetal risk can be defined. Previous methotrexate treatment in women has no harmful effects on subsequent pregnancy outcomes.⁵

Recommendation

Methotrexate is contraindicated in pregnancy and should be discontinued 3 months before conception because of its prolonged retention in the tissues. Women should wait at least one menstrual cycle after discontinuation of methotrexate before attempting to become pregnant. After stopping methotrexate, folic acid supplementation should be continued in the preconception and postconception periods.

Key points

- In patients with rheumatoid arthritis who are planning to become pregnant, remission or substantial improvements in disease activity should be achieved by use of the most effective therapy available
- Potential teratogens or drugs that have not been proven safe for the fetus—including methotrexate, leflunomide, abatacept and rituximab—should be discontinued before pregnancy
- Once pregnancy is recognized, withdrawal of tumor necrosis factor inhibitors and bisphosphonates is advised, owing to a lack of data on the long-term effects of antenatal exposure
- Chloroquine, hydroxychloroquine, sulfasalazine, azathioprine and ciclosporin can be used throughout pregnancy, although many patients opt to discontinue all DMARDs and rely on corticosteroids, NSAIDs and analgesics to manage symptoms
- Inadvertent exposure to potentially fetotoxic drugs is not an absolute indication for pregnancy termination; the decision should be based on careful assessment of the risk to the fetus
- Disease flares can be effectively treated with intra-articular or oral corticosteroids; other options include analgesics and NSAIDs

Leflunomide

Leflunomide has been assigned an FDA pregnancy category X (a proven teratogen). This classification is based on its mechanism of action inhibiting the *de novo* synthesis of pyrimidine in activated lymphocytes. Animal studies in pregnant rats and rabbits demonstrated an increased risk for embryotoxicity and teratogenicity in their offspring, an effect that might be species-specific.¹³ Case reports and small case series have not shown an increase in birth defects in leflunomide-exposed human pregnancies,^{14,15} although one case of a child with cerebral palsy has been reported.¹⁶ The only prospective, controlled study of leflunomide exposure, performed by the Organization of Teratology Information Specialists (OTIS), did not show an increased rate of major birth defects in a group of 63 leflunomide-exposed women with RA compared with a group of 108 women with RA who did not use leflunomide and with a second group of 47 women without RA.¹⁷ A slight increase in prematurity was noted in the infants whose mothers were exposed to leflunomide.¹⁷ Several hundred pregnancies have been registered in the safety database of the manufacturer, without any specific malformation pattern emerging for leflunomide (L. J. Scarazzini [Sanofi–Aventis], personal communication).

Recommendation

Owing to a lack of evidence (85 leflunomide-exposed pregnancies have been studied), whether leflunomide is safe in human pregnancy is still uncertain. Therefore, the conservative approach is to exclude pregnancy before leflunomide treatment and to inform patients to practice reliable contraception during therapy. Owing to the long half-life of the active metabolite of leflunomide, the manufacturer advises stopping leflunomide 2 years before a planned pregnancy or use of a washout procedure.¹⁸ Washout with cholestyramine rapidly lowers the blood level of the active leflunomide metabolite when a

Table 1 | Antirheumatic drugs and biologic agents not to be continued during pregnancy

Drug	Developmental toxicity reported	Recommendation
Methotrexate	Toxic effects in animals and humans	Discontinue 3 months before pregnancy
Leflunomide	Toxic effects in animals No increase in rate of adverse outcomes in 85 human pregnancies	Discontinue when planning pregnancy and washout before pregnancy
Abatacept	Toxic effects in animals No data in human pregnancy	Discontinue 10 weeks before pregnancy
Rituximab	Depletes fetal B cell numbers in animals and humans when administered in second or third trimester	Discontinue 12 months before pregnancy
Infliximab	No toxic effects in animals Sporadic reports of adverse events in humans insufficient to determine toxicity or safety	Discontinue at missed period or after a positive pregnancy test
Etanercept	No toxic effects in animals Sporadic reports of adverse events in humans insufficient to determine toxicity or safety	Discontinue at missed period or after a positive pregnancy test
Adalimumab	No toxic effects in animals Insufficient data in human pregnancy	Discontinue at missed period or after a positive pregnancy test
Bisphosphonates	Toxic effects in animals Insufficient data in human pregnancy	Discontinue at missed period or after a positive pregnancy test

pregnancy is planned or in case of incidental pregnancy during therapy.

Abatacept

Abatacept and rituximab are, at present, not considered first-line therapy for RA, but are reserved for patients who fail to respond to treatment with classical DMARDs and tumor necrosis factor (TNF) inhibitors.¹⁹ Abatacept is a selective costimulation modulator that inhibits the activation of T cells, and is administered as monotherapy or in combination with methotrexate. According to the manufacturer,²⁰ studies in pregnant animals have shown that abatacept crosses the placenta. Treatment of pregnant rats and rabbits with up to 29 times the human dose did not produce malformations in the offspring, although the female offspring of rats treated with a dose 11 times greater than the human dose demonstrated altered immune function (consisting of a ninefold increase in the T-cell dependent antibody response).²⁰

Recommendation

No data of abatacept use in human pregnancy experience has been published; therefore, discontinuation at least 10 weeks before a planned pregnancy is recommended.

Rituximab

Rituximab, a monoclonal, B-cell-depleting antibody of the IgG₁ subclass, crosses the placenta and, at term, achieves fetal serum levels similar to maternal levels.²¹ In animal studies, B-cell depletion in the fetus recovered spontaneously after birth. Human pregnancy experience consists of eight case reports:^{21–27} five pregnancies occurred in women with lymphomas^{22–25} and three in women with hematological diseases.^{21,26,27} The pregnant patients with malignancies were also treated with other cytotoxic drugs. Lymphopenia, but no B-cell depletion, was noted in one of two neonates after first-trimester

exposure to rituximab.^{25,27} Six pregnant mothers were treated during the second and third trimesters. In three cases, serum levels of rituximab were similar in the mothers and their newborns,^{21,23,24} who also had greatly reduced or undetectable numbers of B cells. Spontaneous recovery of B cell numbers occurred within 6 months of birth in the infants. IgG levels were normal in four children in whom such studies were performed, and they all showed a normal response to vaccination.²¹

Recommendation

Whether pre-conception or first-trimester exposure to rituximab exposes the fetus to any risk is unclear. By contrast, second-trimester and third-trimester exposure causes B-cell depletion in the fetus, with unknown long-term effects in the child. The manufacturer recommends discontinuation of rituximab 1 year before a planned pregnancy.²⁸

Drugs suitable for use until conception

TNF inhibitors

Human experience with TNF inhibitors stems from case reports, small case series and some placebo-controlled studies. Excluding women who were treated with anti-TNF agents before conception, and including only women with exposure during pregnancy, more than 200 pregnant patients were exposed to infliximab, more than 100 to etanercept and about 50 to adalimumab.^{29–33} Most were exposed during the first trimester, and only 29 women were treated with TNF inhibitors throughout pregnancy.³³ Significant transplacental passage of the monoclonal antibodies infliximab and adalimumab takes place from the second trimester of pregnancy onwards, and their levels increase in cord blood to reach levels similar to or higher than maternal levels at term.^{34,35} Children have been born healthy after maternal use of infliximab throughout pregnancy.^{33,36} Two prospective,

controlled studies performed by the OTIS group showed similar overall rates of miscarriage and malformations in exposed and non-exposed pregnancies.^{17,32} Preterm delivery and lower-than-normal mean birth weight was significantly more frequent in patients with RA than in non-RA controls, regardless of exposure status. Congenital malformations after exposure to infliximab and etanercept have been reported (too few reports of pregnancy exposures to adalimumab). Up to December 2005, 41 cases of children born with congenital malformations after *in utero* exposure to infliximab or etanercept had been recorded in an FDA database study,^{37,38} including 2 children with VACTER association (V: vertebral malformation; A: anal anomalies; C: cardiac anomalies; T: tracheal problems, E: esophageal problems, R: renal anomalies). Most of the reported anomalies included those that are common in the normal population. However, the FDA study³⁸ had neither the design nor methodology to discern whether the rate of reported congenital anomalies exceed the 3–5% of birth defects expected in the normal population; the total number of pregnancy exposures to TNF inhibitors was not known, nor was a diseased or non-diseased control group included.³⁸ Whether the observed malformations were coincidental to or caused by TNF inhibitors is, therefore, impossible to assess.³⁹

Recommendation

Neither animal studies nor prospective, controlled human studies have shown an increased rate of adverse outcomes after exposure to TNF inhibitors during pregnancy; therefore, TNF inhibitors can be continued until an expected menstruation is missed or after a positive pregnancy test. Owing to very limited experience from treatment throughout pregnancy and an absence of knowledge about the possible long-term effects on exposed children, however, TNF inhibitors should be discontinued as soon as pregnancy is recognized.

Bisphosphonates

Bisphosphonates are frequently prescribed in women of childbearing age with RA for the treatment and prevention of glucocorticoid-induced osteoporosis. Bisphosphonates are incorporated into the bone matrix, have a half-life of up to 10 years, and can, therefore, be mobilized during pregnancy, even if the drug was stopped before conception. Animal studies in rats suggest that bisphosphonates cross the placenta and accumulate in fetal bone. Offspring of rats treated with subcutaneous alendronate during pregnancy at doses similar to human therapeutic doses showed decreased bone growth and reduced birth weight.⁴⁰

Several case reports and two cohort studies have described pregnancy outcomes in mothers treated with bisphosphonates (mostly oral alendronate and pamidronate).^{41–43} One cohort study reported no increased teratogenic risk in 24 infants born to patients with alendronate exposure 6 months before conception ($n = 8$) or in the first 8 weeks of gestation ($n = 15$).⁴² The other

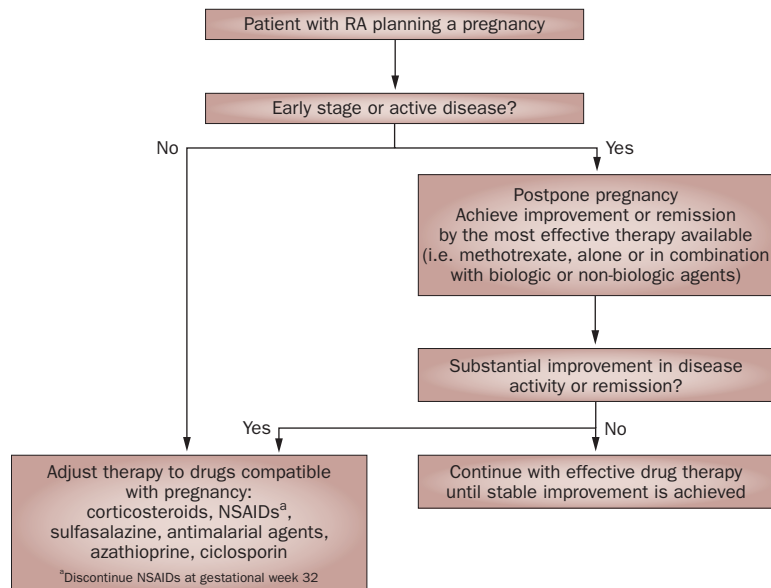


Figure 1 | Algorithm of a treatment strategy for patients with RA planning a pregnancy. In patients with stable disease, or with mild-to-moderate disease activity, therapy should be adjusted from drugs incompatible with pregnancy (e.g. methotrexate) to compatible drugs. In patients with early RA or with active and uncontrolled disease activity, pregnancy should preferentially be postponed until substantial improvement in disease activity or remission is achieved. Once RA is stable, and after a switch to drugs compatible with pregnancy, conception can be attempted. Abbreviations: RA, rheumatoid arthritis; TNF, tumor necrosis factor.

cohort study compared the outcomes of 21 infants born to patients treated with various bisphosphonates (12 with alendronate, 5 with etidronate, 2 with risedronate and 2 with pamidronate) with outcomes in a control group. 15 patients in the bisphosphonate group had first-trimester exposure, and 6 patients discontinued bisphosphonate therapy within the 3 months prior to conception. The risk of abortion, birth defects or growth retardation was not increased with bisphosphonate exposure.⁴³

Recommendation

The limited evidence of bisphosphonate use before and during human pregnancy does not show a significantly increased risk for congenital anomalies. Bisphosphonates given by infusion or injection during pregnancy might lead to hypocalcemia in the neonate. Hypocalcemia did not occur in neonates exposed to oral bisphosphonates;⁴² therefore, oral rather than other formulations of bisphosphonates might be safer for patients planning a pregnancy. In the absence of long-term follow-up data in children exposed to bisphosphonates *in utero*, discontinuing bisphosphonates once pregnancy is recognized is advised.

DMARDs compatible with pregnancy

Once stable improvement is achieved, the patient planning a pregnancy should be advised to switch to a DMARD that is safe for use during pregnancy (Box 1).

Box 1 | Limitations to drug options for pregnant patients with rheumatoid arthritis

The choice of immunosuppressive and biologic agents for a patient with rheumatoid arthritis planning to conceive is limited to those drugs that are compatible with pregnancy. Many highly efficacious combination therapies are contraindicated during pregnancy. Antimalarial agents, sulfasalazine, azathioprine and ciclosporin can be used throughout pregnancy.

Box 2 | Handling inadvertent drug exposure

Inadvertent exposure to potentially fetotoxic drugs is not an absolute indication for termination of pregnancy. Drug dose and timing of exposure are essential to assess the risk of malformations or chromosomal aberrations. The decision for or against continuation of the pregnancy should be made on the basis of the expected risk of harm to the fetus.

Several DMARDs have been studied extensively in the setting of pregnancy (including controlled studies). RA treatment options for the pre-pregnancy patient and the 40–50% of pregnant patients in need of therapy include antimalarial agents, sulfasalazine, gold compounds (rarely used, so not reviewed here), azathioprine and ciclosporin, which can all be used either as monotherapy or in combination with low-dose prednisone. However, many patients decide to stop taking DMARDs altogether and try to conceive without changing to a new DMARD. The efficacy of most classical DMARDs is not apparent until after 3–6 months of use, a delay that might not be acceptable for the pre-pregnancy patient, nor is it suitable for the patient who is already pregnant. For patients who discontinue all DMARDs, only prednisone, NSAIDs and analgesics remain as therapeutic options in case of a relapse.

Chloroquine and hydroxychloroquine

Several studies have examined the effects of antenatal exposure to the antimalarial agents chloroquine and hydroxychloroquine. In a study of 11 mother-child pairs, near-identical concentrations of hydroxychloroquine were detected in maternal and cord blood at term.⁴⁴ Concerns about the safety of using antimalarial drugs during pregnancy were raised by a case report on malformations of the inner ear and other abnormalities after intrauterine exposure to chloroquine 500 mg daily throughout pregnancy in three siblings born of a mother with systemic lupus erythematosus.⁴⁵ However, subsequent retrospective and prospective studies, comprising between 36 and 133 pregnant patients exposed to chloroquine 250 mg daily or hydroxychloroquine 200–400 mg daily during the first trimester, did not find an increase in congenital malformations or cardiac conduction disturbances in the antenatally exposed children.^{46–49} Hydroxychloroquine use has not been associated with congenital malformations, nor have any long-term visual, hearing, growth, or developmental abnormalities been found in children studied after *in utero* exposure.^{47,49}

Recommendation

Antimalarial drugs can be regarded as safe for the fetus. However, hydroxychloroquine should be preferred over chloroquine owing to the much higher number of pregnancies in which its effects have been studied, and also because it is found at lower levels in maternal tissue than is chloroquine.

Sulfasalazine

The majority of studies on sulfasalazine during pregnancy have included women with inflammatory bowel disease (IBD). A national survey of 186 pregnancies in women with IBD treated with sulfasalazine alone or with concomitant steroid therapy found the incidence of fetal morbidity and mortality comparable both to that of 245 untreated IBD pregnancies, and to pregnancies in the general population.⁵⁰ Similarly, a population-based case-control study⁵¹ and a cohort study⁵² found no increase in the rate of birth defects compared with the general population. A meta-analysis compared the outcomes of 2,200 pregnancies in patients with IBD, of which 642 were treated with a mesalazine drug (including sulfasalazine) and 1,558 were untreated. The risk for congenital malformations was not significantly elevated in the mesalazine-exposed group.⁵³ Sulfasalazine belongs to the group of folic acid antagonists, which increase twofold to threefold the rate of oral clefts and cardiovascular anomalies in children exposed antenatally, as shown by the study of Hernandez-Diaz *et al.*⁵⁴ Unfortunately, the number of pregnancies exposed to sulfasalazine in this study was low and, therefore, not analyzed; however, the use of multivitamin agents containing folic acid clearly diminished the adverse effects of all the drugs studied.⁵⁴

Impairment of hematopoiesis has been reported in single cases (fetal hemolytic anemia, aplastic anemia and neutropenia) after prenatal exposure to sulfasalazine.⁴

Recommendation

Sulfasalazine at a dose of 2 g per day may be given throughout pregnancy, but requires folic acid supplementation.

Azathioprine

Azathioprine and ciclosporin are not used as first-line drugs in RA, neither as monotherapy nor in combination therapies. Reasons for this are their lower effectiveness, and, in the case of azathioprine, a higher rate of adverse effects than other DMARDs or biologic agents.⁵⁵ For both drugs, evidence of their use in pregnancy stems mainly from studies of pregnant transplant recipients, who often receive azathioprine, ciclosporin and prednisone concomitantly.⁵⁶ A prospective, case-control study showed no increase in the rate of birth defects in 160 children exposed to azathioprine 50–100 mg per day antenatally compared with that in 200 children of healthy, untreated women.⁵⁷ Prematurity occurred more frequently among children of mothers with different autoimmune diseases, some of whom were transplant recipients, but birth weight adjusted for gestational

Table 2 | Treatment of a flare during pregnancy

Type of flare	Drugs compatible with pregnancy	Precaution
Acute arthritis (i.e. pain and stiffness) in one or several joints	Intra-articular corticosteroids or NSAIDs, including diclofenac, ibuprofen, ketoprofen, mefenamic acid, naproxen, piroxicam	NSAIDs must be discontinued at week 32 of gestation
Pain	Paracetamol (acetaminophen)	1–4 g per day can be safely given throughout pregnancy
Systemic flare	Oral corticosteroids	Restrict to ≤ 15 mg in the first trimester
	Chloroquine or hydroxychloroquine	Hydroxychloroquine preferable to chloroquine because of less tissue distribution
	Azathioprine	Restrict to ≤ 2 mg/kg per day
	Ciclosporin	Monitor and control maternal blood pressure
	Sulfasalazine	Folic acid supplementation required

age did not differ.⁵⁷ A Danish cohort study investigating pregnancy outcomes in women with Crohn's disease found an almost threefold increase in the risk of congenital anomalies following prenatal exposure to azathioprine and 6-mercaptopurine (the active metabolite of azathioprine) compared with untreated patients, although only 20 pregnancies were exposed.⁵⁸

Recommendation

Azathioprine can be used during all stages of pregnancy. The daily dose of azathioprine should not exceed 2 mg/kg because of a risk of depressed hematopoiesis in infants whose mothers are treated with higher doses.⁵⁹

Ciclosporin

The largest database on the use of ciclosporin during pregnancy is the US National Transplantation Pregnancy Registry (NTPR), which comprises data on over 2,400 pregnancies.⁶⁰ The observed rate of 3% congenital malformations in ciclosporin-exposed pregnancies does not exceed the rate reported in the general population. No increase in the neonatal death rate or any recurring pattern of congenital anomalies has been observed in infants exposed to ciclosporin antenatally.⁶¹ A meta-analysis assessing pregnancy outcome after ciclosporin treatment during pregnancy came to the same conclusions.⁶² Renal and liver function were normal in 166 neonates exposed to ciclosporin *in utero*.⁶³

Recommendation

Ciclosporin at a dose of 2.5–5.0 mg/kg per day can be given throughout pregnancy.

Other drugs compatible with pregnancy

Corticosteroids

The influence of corticosteroids on intrauterine growth is controversial, as delineation of drug effects from underlying, often severe, maternal disease is difficult.⁶⁴ Several prospective studies of pregnant RA patients have shown that treatment with 5–15 mg prednisone daily throughout pregnancy does not result in an excess of

low-birth-weight or small-for-gestational-age infants.^{3,65} Prolonged treatment with prednisone exceeding 15 mg daily, however, increases the risk for intrauterine infection and premature delivery.⁶⁶

First trimester exposure to corticosteroids (doses not specified) has been associated with a moderately increased relative risk of oral clefts (reviewed elsewhere).⁶⁷ Park-Wyllie *et al.*⁶⁸ put the risk of oral cleft conferred by corticosteroid use into perspective: the risk is one child with oral cleft per 1,000 live births without any exposure to corticosteroids, which increases to 1.3–3.3 per 1,000 live birth with exposure to corticosteroids in the first trimester.

Recommendation

Corticosteroids can be administered orally or intra-articularly throughout pregnancy. Owing to a moderately increased risk for oral clefts, the daily dose should be the lowest effective dose during the first trimester. Patients on long-term corticosteroid treatment should receive stress doses of prednisone during the peripartum period.

NSAIDs

NSAIDs can impair fertility by inhibiting cyclo-oxygenase (COX)-1 and COX-2, enzymes that are necessary for the rupture of the luteinized follicle. Luteinized unruptured follicle syndrome (LUFS) has been observed after treatment with nonselective and selective COX-2 inhibitors, the latter being more potent inducers of LUFS.^{69–70} However, the frequency of LUFS in women treated with NSAIDs is unknown. Patients who experience infertility should discontinue NSAIDs.

The potential of NSAIDs, including aspirin, to induce birth defects after first-trimester exposure is a matter of debate. Some studies have found an increased risk for cardiac septal defects and gastroschisis in exposed infants; others have not.^{71–73} Two US and two European population-based cohort and case–control studies have assessed the teratogenic risks of first-trimester use of non-selective COX inhibitors, including aspirin. Taken together, several hundred-thousands of pregnancies have

been studied without finding an increased risk of congenital malformations.^{4,74,75} First-trimester use of selective COX-2 inhibitors, such as celecoxib and etoricoxib, in human pregnancy has not been reported.

The inhibition of prostaglandin synthesis by NSAIDs can cause important fetal adverse effects during the second and third trimesters. Constriction or premature closure of the fetal ductus arteriosus is a risk associated with the use of all NSAIDs, and might lead to pulmonary hypertension if the drugs are not promptly withdrawn. The severity of pulmonary hypertension is dose-related,^{76–78} and has been reported after antenatal exposure to aspirin, naproxen, ibuprofen and nimesulide in the third trimester.⁷⁹ The constriction of the ductus arteriosus frequently reverses within 24–48 h after cessation of therapy. Impaired fetal renal function, with a decline in fetal urine output and development of oligohydramnios, has been reported after administration of non-selective and selective COX-inhibitors, and requires immediate discontinuation of maternal therapy.^{80–81} Development of oligohydramnios has been shown to be dose-dependent, but is reversible within 1 week after cessation of maternal therapy.⁸¹

Recommendation

NSAIDs, preferentially those with a short half-life, may be continued until gestational week 32. Notably, in the US withdrawal is recommended at start of the third trimester. Intermittent use of NSAIDs at the lowest effective dose reduces the risk for fetal adverse effects.

Managing inadvertent drug exposure

Compliance with the advice of birth control use is not followed by a substantial proportion of patients.⁸² Consequently, unplanned pregnancies occur during therapy with potentially fetotoxic drugs such as methotrexate. In order to avoid unnecessary termination of pregnancy in women who desire children, careful handling of inadvertent drug exposure during pregnancy is required (Box 2). Information on the dose and exact time of gestational exposure reveals whether the drug has been taken at a critical dose and at a stage of development during which the embryo is susceptible to damage. The characteristic pattern of malformations expected for the drug in question should then be screened for by use

of serial prenatal ultrasonography (at week 11–12 and 18–20) by experienced specialists or at a center specializing in fetal medicine. Chromosomal aberration of fetal cells can be examined by amniocentesis or chorionic villi biopsy. In cases where the results of all these tests are normal, major pathology of the fetus is unlikely to be present.

Treating RA flares during pregnancy

Acute arthritis occurs in about 10–25% of women with RA at some stage of pregnancy.^{2–3} For the patient who has active arthritis in one or a few joints, intra-articular steroid injections may give rapid and lasting relief. A short course of high-dose prednisone (for example, >20 mg daily) with gradual reduction over 2–3 weeks may be equally effective. Other options are analgesics such as paracetamol, NSAIDs (until gestational week 32) or low-dose oral corticosteroids over a prolonged period (Table 2).

Conclusions

The stage and severity of RA must be considered when designing drug therapy for the patient who desires children or who is already pregnant. If possible, remission of RA or stable disease should be achieved before attempting to conceive. Discontinuation of effective therapy when planning a pregnancy could leave the patient without disease suppression for an unknown period of time. If prophylactic withdrawal of possibly fetotoxic drugs is necessary before pregnancy, other therapeutic options must be considered. Immunosuppressive drugs compatible with pregnancy should be chosen in order to avoid a flare of RA during pregnancy or the postpartum period.

Review criteria

A PubMed search of English-language journals from 1980 to December 2008 was performed with the following terms alone or in combination: “rheumatoid arthritis”, “pregnancy”, “congenital malformations”, “fetal toxicity”, and names of specific antirheumatic medications. Additional full-text papers and abstracts were identified from reference lists of relevant articles or from congress proceedings. The authors also used articles from their private libraries.

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