

The Effects of Immunosuppressive and Anti-inflammatory Medications on Fertility, Pregnancy, and Lactation

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Many rheumatic diseases affect women of childbearing age, and the medications used to treat these diseases may affect conception, pregnancy, fetal development, and lactation. Physicians who care for these women need to be aware of the potential adverse effects of these medications, and which medications can be used safely prior to conception and during pregnancy and lactation. Although reviews of individual classes of medications are available, there is no practical and comprehensive review that summarizes all of this information, and includes anticoagulant drugs and 2 recently approved drugs for rheumatoid arthritis. Women who take cytotoxic drugs should be informed of the risks of impaired fertility and congenital malformations, and must use effective methods of contraception. During pregnancy, nonsteroidal anti-inflammatory agents may be used until the last 6 weeks, and low to moderate doses of corticosteroids are safe throughout pregnancy. Among the disease-modifying agents, sulfasalazine and hydroxychloroquine treatment may be maintained. Cytotoxic drugs may be used after the first trimester to treat life-threatening disease. During lactation, prednisone, sulfasalazine, and hydroxychloroquine may be used cautiously. Women using heparin for treatment of antiphospholipid antibody syndrome should take measures to prevent bone loss. Men taking methotrexate, sulfasalazine, cyclosporine, azathioprine, or leflunomide should be apprised of the possibilities of infertility and teratogenicity.

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Rheumatic diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma, and antiphospholipid antibody syndrome are common in women of childbearing age. Virtually all the medications used to treat rheumatic diseases may affect conception, fetal development, pregnancy, and breastfeeding infants. Most drugs, however, are not tested in pregnant women, and are not labeled for use during pregnancy. The lack of readily available information presents a problem for both the physician and the woman, who, once counseled to avoid pregnancy altogether, is now considering motherhood. Physicians who care for these patients need to be aware of the potential adverse effects of these medications, and of which medications can be

used safely prior to conception and during pregnancy and lactation. Although reviews of individual classes of medications are available, there is no practical and comprehensive review that summarizes all of this information. We have summarized the literature on the effects of anti-inflammatory, immunosuppressive, and anticoagulant drugs on fertility, pregnancy, and lactation, and provided guidelines for safe use of these therapeutic agents.

ASPIRIN, NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs), AND CORTICOSTEROIDS

Aspirin

Fertility and Conception. The use of aspirin for rheumatoid arthritis has decreased markedly since the introduction

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of various NSAIDs; however, aspirin remains among the most frequently ingested drugs during pregnancy. Aspirin can cross the placenta and cause congenital anomalies in animals, but these are rare in humans. Several large prospective studies failed to confirm a significant increase in cleft palate or congenital anomalies.^{1,2}

Pregnancy: Maternal Effects. High doses of aspirin (3 g/d or more) inhibit uterine contractility and prolong labor and gestation. Mothers taking aspirin regularly were more anemic and had a prolonged gestation, more complicated deliveries, and an increased incidence of both antepartum and postpartum hemorrhage.^{3,4,5} Low-dose aspirin, used as an antiplatelet agent, seems to be safe throughout pregnancy, and has been used for patients with SLE, antiphospholipid antibody syndrome, and recurrent fetal loss. There are possible benefits of low-dose aspirin for patients at risk for the development of pregnancy-induced hypertension and preeclampsia, and in fetuses with intrauterine growth retardation, but studies do not yet adequately define the risk-benefit ratio of such therapy.^{6,7}

Pregnancy: Fetal Effects. Possible premature closure of the ductus arteriosus in the fetus is a concern, and has been postulated to occur in some cases of stillbirth associated with chronic or intermittent use of high-dose aspirin.^{8,9} Use of full doses of aspirin near the time of birth can cause decreased platelet aggregation in the fetus, and may increase the risk of intracranial hemorrhage in premature or low-birth-weight infants.¹⁰ Transient neonatal renal failure and oligohydramnios also have been described.¹¹

Lactation. The presence of substantial serum salicylate levels have been demonstrated in breastfed neonates, which raises concerns about metabolic acidosis, bleeding, altered pulmonary circulation, and Reye syndrome. After a single aspirin dose of 450 to 650 mg, 0.1% to 21% reaches the infant over a 24-hour period.¹² Peak salicylate concentrations in milk occur about 2

hours after peak serum levels. However, with chronic maternal intake of anti-inflammatory doses and immature neonatal metabolism, the infant can potentially develop salicylate intoxication and bleeding problems. Further, the infant can absorb free salicylic acid from the cleavage of salicylphenolic glucuronide in milk.¹³ The American Academy of Pediatrics recommends that aspirin be used cautiously by the mother of the nursing infant, and large doses should be avoided.¹⁴

Recommendations. Anti-inflammatory doses of aspirin should be avoided during the last 4 to 8 weeks of pregnancy to avoid prolonged gestation and labor, increased maternal and fetal bleeding during delivery, and possible premature closure of the ductus arteriosus. Some possible uses remain for low-dose aspirin therapy as an antiplatelet agent, especially for women with recurrent fetal loss. Nursing mothers should avoid large doses of aspirin.

Nonsteroidal Anti-inflammatory Drugs

Conception and Fertility. The use of NSAIDs in pregnancy has not been investigated in depth for many of the newer agents. These drugs are not known to be teratogenic in humans, and prophylactic cessation of therapy is not necessary.¹⁵ Women attempting to conceive, however, should not use any prostaglandin synthesis inhibitors because of the findings in a variety of animal models that indicate these agents block blastocyst implantation.¹⁶

Pregnancy: Maternal Effects. Possible effects on the mother include prolonged gestation and labor, increased peripartum blood loss, and increased anemia. These problems are rare if NSAID treatment is discontinued 6 weeks before term.¹⁷

Pregnancy: Fetal Effects. As with aspirin, the potential adverse effects of NSAIDs on the fetus include increased cutaneous and intracranial bleeding, premature closure of the ductus arteriosus, pulmonary hypertension, impaired renal function, a reduction in urine output, and

reduced amniotic fluid volume. These effects have been demonstrated for indomethacin, naproxen, ketoprofen, and ibuprofen, and may also occur with other prostaglandin synthesis inhibitors. The dose, duration, and period of gestation are important determinants of these effects. It is believed that these effects are uncommon with cessation of therapy 6 to 8 weeks before delivery.^{15,17-20}

Lactation. Although most NSAIDs do not achieve high concentrations in breast milk, they should be used with caution by nursing mothers. Trace amounts of naproxen, piroxicam, ibuprofen, and diclofenac have been reported in milk. Some of the NSAIDs circulate enterohepatically (indomethacin, sulindac) and should be avoided. Because most NSAIDs displace bilirubin, they can increase the risk of kernicterus and are contraindicated in the jaundiced neonate. The American Academy of Pediatrics considers ibuprofen, indomethacin, and naproxen to be compatible with breastfeeding.¹⁴ A case report of possible indomethacin-induced seizures in a breastfed infant has been published, although the causal link between the 2 events was not proven.²¹

Recommendations. When administered to the pregnant patient, NSAIDs should be given in the lowest effective dose, intermittently if possible, and treatment should be discontinued at least 6 to 8 weeks prior to expected delivery. Some published studies suggest that in selected patients, an NSAID with a short half-life and inactive metabolites, such as flurbiprofen, diclofenac, or ibuprofen, may be used more safely.²²⁻²⁵ Nonsteroidal anti-inflammatory drugs may be used with caution by nursing mothers, and the use of acetaminophen as an analgesic should be considered as an alternative.

Corticosteroids

Corticosteroids are potent anti-inflammatory drugs that are used in many patients with rheumatic diseases, and they are often the mainstay of therapy in pregnant pa-

tients. When glucocorticoids are needed to treat fetal conditions such as immature lungs, fluorinated preparations such as dexamethasone and betamethasone are preferred because they are less well metabolized by the placenta and greater doses are available to the fetus.

The shorter-acting agents, prednisone, prednisolone, and methylprednisolone, are metabolized by placental 11-hydroxygenase, and the fetus is exposed only to approximately 10% of the maternal dose. These glucocorticoids are preferred for the treatment of maternal disorders.²⁶

Fertility and Conception. Other than the impact of the underlying maternal disease, the use of corticosteroids prior to pregnancy does not seem to adversely impact fertility (**Table**). Corticosteroids in high doses have caused cleft palate in experimental animal models and low birth weight in humans.^{27,28} However, there is no evidence that either prednisone or methylprednisolone are teratogenic in humans (Food and Drug Administration [FDA] risk category B). (The FDA risk categories are: [A] controlled studies in women fail to demonstrate a risk to the fetus in the first

trimester [and there is no evidence of a risk in the later trimesters], and the possibility of fetal harm seems remote; [B] either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect [other than a decrease in fertility] that was not confirmed in controlled studies in women in the first trimester [and there is no evidence of a risk in later trimesters]; [C] either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus; [D] there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk [eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective]; and [X] studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant

women clearly outweighs any potential benefit. The drug is contraindicated in women who are or may become pregnant.) A large retrospective study of corticosteroid-treated pregnant patients with asthma failed to show an increased incidence of birth defects compared with the general population. Most women were receiving low-dose prednisone (mean daily dose of 8 mg) and were taking glucocorticoids at the time of conception.²⁹

Pregnancy: Maternal Considerations. The complications associated with the use of corticosteroids in a pregnant patient are the same as in those that may occur in nonpregnant patients, including immunosuppression, avascular necrosis of bone, osteopenia, hypertension, hyperglycemia, cataracts, and striae. However, there may be pregnancy-specific complications such as premature rupture of the membranes and exacerbation of gestational diabetes and hypertension.³⁰

Pregnancy: Fetal Considerations. Effects of high-dose pulse therapy during pregnancy have not been determined, although it has been reported that fetal movements are transiently decreased following the administration of high-dose fluorinated steroids.³¹ Only a small percentage of the maternal dose of short-acting glucocorticoids reaches the fetus; however, for the glucocorticoid-exposed neonate, monitoring for adrenal suppression and infection is important. Fortunately the incidence of adrenal suppression and infection seems to be quite low.^{32,33}

Lactation. Small amounts of glucocorticoids can be present in the breast milk of women taking these medications. However, no adverse effects have been reported, and the American Academy of Pediatrics has declared prednisone and prednisolone safe and compatible with breastfeeding.¹⁴ No data are available on the use of dexamethasone or betamethasone in lactating women.

Recommendations. The routine use of oral calcium and vitamin D supplements is recommended to

Antirheumatic and Immunosuppressive Drugs Recommended During Pregnancy and Lactation*				
Recommended Drug	FDA Risk Category†	Conception‡	Pregnancy	Breastfeeding
Mild Symptoms				
Aspirin	C (D, third T)	Compatible	d/c 6-8 wk before expected delivery	Compatible
NSAIDs§	B (C, high dose) (D, near term)	Compatible	d/c 6-8 wk before expected delivery	Compatible
Moderate Symptoms				
Corticosteroids	B	Compatible	IUGR	Compatible
Hydroxychloroquine	C	Compatible	Compatible	With caution
Sulfasalazine	B (D, near term)	Compatible	Compatible	With caution
Severe or Life-Threatening Disease				
Azathioprine	D	Compatible	IUGR	Contraindicated
Cyclosporin A	C	Compatible	IUGR	Contraindicated
Cyclophosphamide	D	Avoid	Avoid, first T	Contraindicated

*FDA indicates Food and Drug Administration; T, trimester; d/c, discontinue; NSAID, nonsteroidal anti-inflammatory drug; and IUGR, intrauterine growth retardation.

†See text at the table citation for explanations of the FDA codes.

‡No congenital anomalies were reported or too few cases were reported to ascribe a cause-effect relationship with the use of the drug prior to conception or in early pregnancy.

§Diclofenac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam. (Diflunisal, etodolac, ketorolac, mefenamic acid, nabumetone, oxaprozin, oxyphenbutazone, phenylbutazone, and tolmetin are FDA risk categorized as C/D.)

||Prednisone and methylprednisolone.

help prevent osteoporosis. The lowest possible dose needed to control disease activity should be used, and a patient who has been treated with corticosteroids during pregnancy should be given "stress doses" of hydrocortisone for any emergency surgery, cesarean section, or prolonged labor and delivery. Neonates should be monitored for evidence of adrenal insufficiency and infection. Women who choose to breast-feed while taking high doses of glucocorticoids could wait 4 hours after ingesting a dose to resume breast-feeding, a strategy that will decrease the amount of glucocorticoid in the milk.^{14,34}

CYTOTOXIC DRUGS

Cyclophosphamide

Fertility and Conception. Daily oral cyclophosphamide causes amenorrhea within a year, usually with permanent ovarian failure in over 70% of patients. Monthly intravenous pulse cyclophosphamide also can cause amenorrhea in up to 45% of patients, depending on the dose and timing with regard to the menstrual cycle. The risk of amenorrhea is greatest in women older than 31 years. Patients receiving 7 doses of intravenous cyclophosphamide had a 12% frequency of amenorrhea compared with 39% who underwent long-term therapy (more than 15 doses).³⁵ It has been suggested that the administration of monthly intravenous cyclophosphamide be timed during menses. However, it is during the earliest follicular phase that young follicles are being recruited, and this strategy alone is not likely to be sufficient. Other options include the use of oral contraceptives or gonadotropin-releasing hormone agonists, which inhibit ovulation and are believed to protect ovarian follicle viability. If time permits, another alternative is cryopreservation of oocytes.³⁶ Treatment of pregnant patients with cancer with cyclophosphamide has demonstrated substantial teratogenicity, especially when administered in the first trimester. Patients undergoing therapy with cyclophosphamide must be counseled to avoid pregnancy and to use adequate contraception.

Pregnancy: Fetal Effects. Teratogenicity, impaired growth, bone marrow suppression, infection, hemorrhage, and the long-term effects on the fetal genome are of concern. Both normal and malformed newborns have been reported after the use of cyclophosphamide in pregnancy. The reported malformations involve the skeleton, palate, limbs, and eye, and are often difficult to detect prenatally.³⁷ Impaired fetal growth has been reported, but seems to be multifactorial in etiology, and due not only to the use of cyclophosphamide, but also other cytotoxic drugs and the underlying maternal disease.³⁸ Use of cyclophosphamide in the second and third trimesters does not seem to place the fetus at risk for congenital defects, and may be considered for the woman with life-threatening rheumatic disease. Except in a few individual cases, long-term studies on fetuses exposed to cyclophosphamide during the second trimester, the period of neuroblast multiplication, have not been conducted.³⁹

Lactation. Cyclophosphamide is found in substantial concentrations in human breast milk.⁴⁰ Nursing is contraindicated in a mother who requires this drug.¹⁴

Recommendations. Cyclophosphamide is generally contraindicated for treatment of rheumatic diseases during pregnancy and lactation. It should be withdrawn at least 3 months before the patient tries to conceive. For the woman who may desire pregnancy at a later time, consideration should be given to preserving ovarian follicle reserve by the timing of intravenous cyclophosphamide administration, use of oral contraceptives, use of gonadotropin-releasing hormone agonists, and/or cryopreservation of oocytes.³⁶ For the patient with life-threatening rheumatic disease, the use of cyclophosphamide may be considered after the first trimester. Offspring should be monitored for immunosuppression and the development of a secondary malignancy.

Chlorambucil

Fertility and Conception. There is evidence that chlorambucil im-

pairs fertility, although the number of patients studied is small.⁴¹ It would be prudent to apprise patients who plan to become pregnant of this risk. As discussed above, measures to preserve ovarian function should be considered.

Pregnancy: Fetal Effects. Chlorambucil is both mutagenic and carcinogenic. The FDA places chlorambucil in risk category D. There have been reports of both normal and malformed infants born who were exposed to chlorambucil in utero.⁴² The use of chlorambucil has been associated with congenital abnormalities including renal agenesis, ureteral malformations, and cardiovascular anomalies.⁴³ As with cyclophosphamide, long-term studies of growth and mental development in offspring exposed to chlorambucil during the second trimester, the period of neuroblast multiplication, have not been reported.

Lactation. There is no information available on the use of chlorambucil during lactation. Treatment with chlorambucil should preclude breastfeeding.

Recommendations. Women of childbearing age who require chlorambucil to control their rheumatic disease should be apprised of the risk of impaired fertility and the imperative to avoid pregnancy. Measures to protect ovarian function in those women who desire pregnancy in the future include the use of oral contraceptives and the use of gonadotropin-releasing hormone.

Azathioprine

Fertility and Conception. Many pregnant patients with renal transplants, hematologic malignancies, inflammatory bowel disease, and SLE have been treated with azathioprine. The drug does not seem to be teratogenic in humans.⁴⁴ Although sporadic anomalies have been reported, no definite association between the drug and the observed abnormalities has been established. There seems to be no effect on fertility and no reported increase in abortion.

Pregnancy: Fetal Effects. Azathioprine crosses the placenta, but the

fetal liver lacks the enzyme that converts azathioprine to its active metabolites. This fetal enzyme deficiency seems to protect the fetus from any teratogenic effects of azathioprine early in pregnancy. With exposure throughout pregnancy, a variety of adverse effects have been described, including fetal growth retardation, decreased thymic shadow, adrenal hypoplasia, depressed serum immunoglobulin levels, and chromosomal abnormalities that may persist for up to a year.³⁷ The incidence of intrauterine growth retardation in women with renal transplants was approximately 40%, possibly due in part to the mother's underlying disease.^{45,46} Infections with cytomegalovirus and gram-negative bacteria have been reported. On the other hand, there have been reports of normal pregnancies and neonates in patients with SLE or renal transplants who were treated with azathioprine and prednisone.⁴⁷⁻⁵⁰

Lactation. Low concentrations of azathioprine are found in breast milk. Nursing is not recommended because of the long-term potential of immunosuppression and carcinogenesis.¹⁴

Recommendations. Patients using azathioprine should use adequate contraception. Because of the potential for carcinogenesis and the unknown long-term effects of fetal immunosuppression, use of azathioprine should be reserved for pregnant women whose rheumatic diseases are severe or life-threatening. Reduction of the azathioprine dose at 32 weeks' gestation may prevent serious neonatal leukopenia and thrombocytopenia.⁵¹ Close prenatal monitoring for growth and long-term evaluation of the offspring are essential.

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDs)

Methotrexate

Methotrexate is a folic acid antagonist used in the treatment of cancer, psoriasis, and many rheumatic diseases. It is the most commonly used DMARD for rheumatoid arthritis in North America, and is usu-

ally administered orally at a dose of 5 to 20 mg/wk. Folate should be routinely supplemented in patients using methotrexate.

Fertility and Conception. Methotrexate does not seem to adversely affect female fertility.^{41,52} Methotrexate therapy can cause reversible sterility in men, as documented in individual case reports (patients often receiving other chemotherapeutic drugs as well).⁵³⁻⁵⁵ Methotrexate is embryotoxic, so women of child-bearing age using methotrexate must be using adequate contraception. Women who wish to become pregnant should discontinue treatment with the drug for at least 3 months prior to attempting conception. Because folate may be depleted during methotrexate use, and folate deficiency is associated with neural tube defects, it is especially important to supplement this vitamin.

Pregnancy: Fetal Considerations. The experience with methotrexate in human pregnancy is mostly limited to patients receiving chemotherapy for cancer and those who have taken the drug to terminate pregnancy.⁵⁶ Many of the cancer cases involve underlying diseases and exposure to other chemotherapeutic drugs as well. On the basis of this collective experience, methotrexate is contraindicated in pregnancy (FDA risk category X) because of severe adverse effects on both the fetus and the course of the pregnancy.

Methotrexate-induced congenital defects are similar to those produced by another folic acid antagonist, aminopterin. The most characteristic malformations induced by methotrexate include craniofacial and limb defects and central nervous system abnormalities including anencephaly, hydrocephaly, and meningomyelocele.^{57,58} Myelosuppression (in 2 cases, with exposure to other antineoplastic drugs as well)^{59,60} and a rare pulmonary disorder, desquamating fibrosing alveolitis, have also been reported.³⁷

In a report of 10 pregnancies in women who received low-dose methotrexate for various rheumatic diseases, there were 5 abor-

tions (3 spontaneous and 2 elective). However, no congenital anomalies were present in the 5 babies who were born at term, and their long-term follow-up also revealed no apparent growth, developmental, or intellectual problems.⁶¹ The authors⁶¹ suggested that the lack of congenital abnormalities in that group of patients could be due to a combination of the low doses of methotrexate used and the folic acid supplementation. However, low doses of methotrexate have been reported elsewhere to cause human malformations.^{62,63}

Lactation. Breastfeeding during methotrexate treatment is not recommended because the drug is excreted into breast milk in low concentrations and may accumulate in neonatal tissues. The American Academy of Pediatrics considers methotrexate to be contraindicated during breastfeeding because of several potential problems, including immune suppression, neutropenia, adverse effects on growth, and carcinogenesis.¹⁴

Recommendations. During treatment with methotrexate, patients should receive supplemental folic acid. Strict attention to contraception is advised. Should the patient desire pregnancy, both she and the potential father should discontinue treatment with the drug at least 3 months before conception because of its prolonged retention in the tissues after discontinuation. Despite reports of some successful outcomes after exposure to methotrexate during early pregnancy, the numbers are too small to draw significant conclusions on the safe use of this drug. Further, the abnormalities that are seen are difficult to detect antenatally. Therefore, methotrexate is contraindicated in a patient who desires to conceive as well as during pregnancy and breastfeeding.

Sulfasalazine

Sulfasalazine is an effective treatment for rheumatoid arthritis, either alone or in combination with other drugs. About 30% of an oral dose is absorbed in the small intestine; the rest passes into the colon

where bacterial azoreductases cleave it into 5-aminosalicylic acid and sulfapyridine. Sulfasalazine and sulfapyridine readily cross the placenta, and fetal concentrations are approximately the same as maternal concentrations. 5-Aminosalicylic acid has very limited placental transfer.⁶⁴

Fertility and Conception. There are no reports of problems with fertility in women taking sulfasalazine. In men, sulfasalazine induces oligospermia, impaired sperm motility, and an increase in the number of abnormal spermatozoa. These effects can result in temporary infertility, which has been shown to be reversible when treatment with the drug is discontinued.^{65,66}

Pregnancy: Fetal Effects. Most data on sulfasalazine in pregnancy are derived from experience with patients treated with this drug for inflammatory bowel disease. In such patients, sulfasalazine does not seem to cause an increase in either the incidence of fetal abnormalities or spontaneous abortions.⁶⁷

Lactation. Sulfapyridine is excreted into breast milk. Milk concentrations are approximately 40% to 50% of maternal serum levels. No adverse effects occurred in 16 nursing infants.^{64,68,69} One infant developed bloody diarrhea attributed to his mother's sulfasalazine therapy. The mother was a slow acetylator who had relatively high blood levels of sulfapyridine.⁷⁰ Based on this report, the American Academy of Pediatrics classifies sulfasalazine as a drug that should be given with caution to nursing women because substantial adverse events may occur in some infants.¹⁴ Anecdotal experience in women with inflammatory bowel disease suggests that sulfasalazine is compatible with nursing.

Recommendations. There is no reason to believe that the safety of sulfasalazine in pregnant women with arthritis would prove to be different from its safety in pregnant women with inflammatory bowel disease. Therefore, sulfasalazine can probably be continued during pregnancy. Indeed, of all the DMARDs, it may be the first choice in treating

rheumatic diseases in women of childbearing age who are planning to become pregnant or are already pregnant.

Hydroxychloroquine

This antimalarial drug is used either alone or in combination with other DMARDs in rheumatoid arthritis. It is also used to prevent flares in patients with SLE.⁷¹

Fertility and Conception. There are no reports of adverse effects of hydroxychloroquine on fertility.

Pregnancy: Fetal Considerations. Hydroxychloroquine crosses the placenta and in theory could accumulate in the fetal uveal tract. To date, however, there have been no reports of congenital malformations in children exposed to this drug used to treat either SLE or rheumatoid arthritis. Parke and West⁷² reported 9 pregnancies in 8 patients with lupus who continued hydroxychloroquine treatment throughout pregnancy. There were 9 live births (4 full term and 5 preterm) with no congenital abnormalities during a mean follow-up of 33 months. Parke and West⁷² concluded that it is safer to continue treatment with hydroxychloroquine than to discontinue it during pregnancy and risk a flare of the disease. In the largest series used to study effects of this drug in pregnancy, Buchanan et al⁷³ reviewed retrospectively the outcomes of 36 pregnancies in 33 patients with lupus exposed to hydroxychloroquine and compared them with pregnancies in 53 control women; the obstetric outcomes of the 2 groups was similar. Furthermore, there was no evidence of teratogenic effects of hydroxychloroquine.

Maternal Considerations. The available data suggest that hydroxychloroquine can be continued safely throughout pregnancy.^{72,74,75} It seems that because of the risk of lupus flare, discontinuing therapy during pregnancy represents a greater danger to the fetus and mother than continuing it. Moreover, cessation of therapy at the time pregnancy is detected would not stop exposure of the em-

bryo and fetus to the drug because of the very long elimination half-life of the drug from maternal tissues.⁷⁶

Lactation. Low concentrations of hydroxychloroquine are found in breast milk. Because of the slow elimination rate and potential for accumulation of a toxic amount in the infant, breastfeeding during daily therapy with hydroxychloroquine should be undertaken cautiously. The American Academy of Pediatrics classifies the drug as compatible with breastfeeding.¹⁴

Recommendations. Hydroxychloroquine does not seem to pose a significant risk to the fetus, especially with lower doses. It may be most prudent to avoid its use during pregnancy in patients with RA, since these patients can be managed safely with corticosteroids. However, for patients with SLE already taking hydroxychloroquine, the benefits of continuing treatment with this medication throughout pregnancy seem to outweigh the risks associated with its use.

Gold

Fertility and Conception. There are limited reports of pregnancy outcomes in women taking gold compounds for the treatment of rheumatoid arthritis.³⁷ Gold does not seem to impair fertility. Most rheumatologists advise women taking gold compounds to use adequate contraception. One approach for patients undergoing long-term parenteral gold therapy is to time each monthly injection on the first day of menses. Such a regimen assures that gold can be withdrawn, if the patient chooses, as soon as pregnancy is recognized.

Pregnancy: Fetal Effects. Gold compounds cross the placenta^{77,78} and have been found in the fetal liver and kidneys. There is no evidence of an increase in neonatal malformations in the small number of pregnancies reported.

Lactation. Gold is excreted in milk and absorbed by the nursing infant. There are a small number of re-

ports of rash, nephritis, hepatitis, and hematologic problems reported, and it is difficult to ascribe a cause-effect relationship. The American Academy of Pediatrics considers gold salts to be compatible with breastfeeding, but because of the prolonged retention of gold in the mother's body and the potential for toxic effects in the infant, it may be most prudent to avoid nursing.⁷⁹

Recommendations. Because RA frequently improves during pregnancy, the potential risks of the drug seem to outweigh the benefits. Nonetheless, in a patient who is stable on gold therapy, many rheumatologists are reluctant to risk a flare either during or after pregnancy and may wish to have these patients continue taking the drug. In that case, a careful discussion with the patient and monitoring of the pregnancy are essential.

Cyclosporine

Experience with cyclosporine in the treatment of rheumatoid arthritis is limited, although it is approved by the FDA for this use. Most of the pregnancy outcome data are from pregnant transplant recipients. Only a few patients with SLE have been reported.^{80,81}

Pregnancy: Maternal Effects. A total of 51 pregnancies in 48 women treated with cyclosporine during pregnancy have been reported, and 11 pregnancies have been conceived from men receiving the drug.⁸² Only 1 of these patients had SLE. Hypertension, pyelonephritis, uterine dystonia, diabetes, seizures, encephalopathy, and a rise in creatinine levels complicated almost half of these high-risk pregnancies.

Pregnancy: Fetal Effects. In the same study of 51 pregnancies, 2 spontaneous and 6 elective abortions occurred, 1 for fetal anencephaly. Of the 43 deliveries, 15 were premature, and 17 required forceps or cesarean section. The mean birth weight was low for more than half of the newborns, but on follow-up only 1 of 20 had slight growth retardation. Seven neonates had vari-

ous other problems, including jaundice, cytopenias, mild disseminated intravascular coagulation, hypoglycemia, intracerebral hemorrhage, and oxygen dependence for 2 days.⁸²

Lactation. Cyclosporine is excreted into human milk, and the American Academy of Pediatrics considers cyclosporine to be contraindicated during lactation because of the potential long-term effects of immune suppression, neutropenia, and a potential association with carcinogenesis.¹⁴

Recommendations. In general, cyclosporine is contraindicated in the treatment of rheumatic disease during pregnancy, and the patient of childbearing age using cyclosporine to treat rheumatic disease should use adequate contraception. The decision to continue treatment with the drug in a stable patient depends on the need for disease control, and it should be made jointly with the patient while weighing the potential risks and benefits. Although there was no increased risk of congenital anomalies in the exposed fetuses reported, the number of cases is small and the long-term effects of cyclosporine exposure in utero are unknown. Of the few newborns reported with anomalies, no consistent pattern of congenital defects occurred, which makes antenatal detection difficult. Breastfeeding should be discouraged in women using cyclosporine.

Penicillamine

Penicillamine is used to treat rheumatoid arthritis and systemic sclerosis. Teratogenicity and skin laxity have been observed in animal studies,⁸³ and exposure of the human fetus to penicillamine has resulted in serious disorders of connective tissue, including cutis laxa, hernias, dislocated hips, and growth retardation.⁸⁴ In general, other drugs such as NSAIDs or low doses of corticosteroids are effective and safer than penicillamine for the pregnant or lactating patient with RA. Its role in pregnancy for women with systemic sclerosis is unknown. Treatment should be discontinued before conception or as soon as pregnancy is confirmed.

Leflunomide

There is very little pregnancy experience with leflunomide, a pyrimidine synthesis inhibitor that was recently approved as a DMARD for RA. It is rated category X by the FDA. Animal data suggest that leflunomide may increase the risk of fetal death or teratogenic effects, and women must not be pregnant when starting treatment with leflunomide. In addition, patients must use reliable contraception during the course of treatment. If treatment is discontinued because of toxic side effects or lack of efficacy, or if the woman wishes to become pregnant, leflunomide treatment must be discontinued and the drug elimination procedure followed.⁸⁵

In this procedure, 8 g of cholestyramine is given 3 times daily for 11 days, followed by 2 separate tests to verify low plasma levels. If blood levels remain high, more cholestyramine may be given. Without the drug elimination procedure, it may take up to 2 years to reach levels safe for pregnancy owing to individual variation in drug clearance.⁸⁵

Etanercept

Another recently approved DMARD for RA, etanercept is a soluble tumor necrosis factor receptor. It is used for patients with moderately to severely active RA with an inadequate response to one or more DMARDs. There is little pregnancy experience with etanercept. Based on short-term studies in rats and rabbits, the FDA has labeled this drug as Class B, for use in pregnancy only if clearly needed. The effects on fertility, carcinogenesis, and nursing are unknown. Although the product labeling does not instruct the patient or physician to obtain negative pregnancy test results before starting treatment, it is prudent to do so. The physician should also advise the patient to use contraception during treatment. In addition, because many drugs and immunoglobulins are excreted in human milk, and because there is potential for serious adverse reactions in nursing infants, a decision should be made to stop nursing or to discontinue treatment with the drug.⁸⁶

HEPARIN AND LOW-MOLECULAR-WEIGHT HEPARIN (LMWH)

The antiphospholipid syndrome (APS), a disorder characterized by recurrent arterial or venous thromboembolic events or recurrent fetal loss, is best treated with lifelong anticoagulation. However, coumarin derivatives cross the placenta and result in substantial problems for the fetus and newborn,⁸⁷ including embryopathy (fetal warfarin syndrome), central nervous system defects, spontaneous abortion, stillbirth, prematurity, and hemorrhage. Thus, patients with APS who are undergoing warfarin therapy must discontinue it prior to conception, and begin anticoagulation treatment with either heparin or LMWH for the course of the pregnancy. Patients with APS manifested by recurrent abortion can be treated either with prednisone or heparin/LMWH plus low-dose aspirin.⁸⁸ In view of the many adverse effects associated with long-term use of prednisone, heparin or LMWH is preferred, unless there is another reason to use prednisone.

Pregnancy. Heparin seems to be safe for the mother and fetus, does not cross the placenta, and has not been associated with congenital defects.⁸⁹ Likewise, even the LMWHs dalteparin and enoxaparin still have relatively high molecular weights and are not expected to cross the placenta. Reports of subcutaneous injections and continuous intravenous infusions of LMWH reveal no evidence of heparin activity in the fetuses or neonates.⁹⁰⁻⁹²

Lactation. Heparin is not excreted into breast milk because of its high molecular weight, and would be safe for a nursing infant. The LMWHs still have a relatively high molecular weight, and would not be expected to be excreted into human milk. Any amounts ingested would likely be inactivated in the gastrointestinal tract, and both unfractionated and LMWH seem to pose little risk to a nursing infant.

Recommendations: Bone density loss normally occurs during preg-

nancy and is aggravated by the use of unfractionated heparin.^{93,94} Adequate calcium and vitamin D intake, along with weight-bearing exercise, is important. Low-molecular-weight heparin has some advantages over unfractionated heparin, including fewer injections, less frequent blood monitoring, and a lower incidence of thrombocytopenia, but osteoporosis and fractures are still reported in women treated with LMWH during pregnancy.⁹⁵ However, 2 small studies of dalteparin found no increase in osteoporosis compared with pregnant controls.^{91,96}

THE MALE PATIENT WITH RHEUMATIC DISEASE

The male patient with rheumatic disease is overlooked in most discussions of reproduction and drug safety. There is little information available regarding the outcome of children born to men taking anti-rheumatic and immunosuppressive drugs, but preconception counseling remains important. The major issue is infertility. Reports on teratogenicity are rare and a cause-effect relationship is difficult to confirm.

Most of the cytotoxic medications can affect male hormone levels and spermatogenesis. A study published in 1985 examined 30 men who were treated as children with cyclophosphamide. Four of the men were azoospermic, 9 were oligospermic, and those who had normal sperm counts had lower sperm density, decreased motility, and less normal sperm forms.⁹⁷ There are isolated reports of congenital anomalies in infants associated with paternal use of cyclophosphamide,⁹⁸ but a direct relationship is difficult to prove because of the lack of experimental evidence and confirming reports.

Azathioprine seems to be safe for men who are attempting to father children. In a report of 57 pregnancies with fathers exposed to azathioprine at conception, 56 infants were normal. There were 3 spontaneous abortions, and 1 infant had a neural tube defect.⁸²

Methotrexate can cause reversible sterility in men, as documented in individual case reports.

The reported patients were often receiving other chemotherapeutic drugs as well.⁵³⁻⁵⁵ Men and women should discontinue methotrexate treatment at least 3 months before conception because of its prolonged retention in the tissues.

Sulfasalazine induces oligospermia, impaired sperm motility, and an increase in the number of abnormal spermatozoa. These effects can result in temporary infertility, which has been shown to be reversible when sulfasalazine treatment is discontinued.^{65,66}

Of the 11 pregnancies fathered by men taking cyclosporine, 2 resulted in spontaneous abortions, and 2 pairs of twins were born. The 11 neonates were healthy.⁸²

The experience of men taking leflunomide who father children is limited. According to the manufacturer, the available information does not suggest that leflunomide would be associated with an increased risk of male-mediated fetal toxic effects. To minimize any possible risk, men wishing to father a child should consider discontinuing treatment with the drug and taking instead 8 g of cholestyramine 3 times daily for 11 days.⁸⁵ Low blood drug levels should be verified prior to conception.

COMMENT

There are no absolute answers regarding the safety of drugs during pregnancy or nursing, since experience in humans is usually anecdotal. Most information comes from voluntary postmarketing surveys or case reports, which are subject to numerous potential selection biases. Experiments with animals have provided considerable information concerning the teratogenic effects of drugs, but these findings cannot be freely extrapolated from animals to humans. Even though it is most prudent to avoid all medications during pregnancy and the preconception period, the use of an antirheumatic drug is frequently necessary for women of childbearing potential to ensure a smooth course for both the mother and fetus.

Although about half of all pregnancies in the United States are unplanned, in the patient with rheu-

matic disease it is especially important to begin a dialogue long before conception is attempted. Counseling should address the use of contraception if appropriate, optimization of the mother's health status before conception, and the avoidance of potentially toxic medications if the patient indicates a desire to conceive. Women with active rheumatic diseases should not have unplanned pregnancies, and so contraception should be addressed with every woman of childbearing age. If women who are to undergo a course of chemotherapy indicate a desire to have children in the future, a thoughtful discussion should take place of the options available to preserve ovarian function.³⁶

From the 1930s to 1960s, there was a dramatic decline in the percentage of American mothers who breastfed their infants. Now, however, a number of surveys indicate that more than 50% of babies are breastfed at the time of hospital discharge, and that number may be increasing. The American Academy of Pediatrics emphasizes breastfeeding as the best nutritional mode for infants for the first year of life, and many women are aware of this recommendation. This interest in breastfeeding has led many mothers to actively question their physicians and pharmacists about the safety and potential toxicity of medications taken by the mother. Although it would be easiest to simply recommend that a mother who requires any medication for her rheumatic disease not nurse, such a simple answer is likely to be questioned by the mother. Objective information of the efficacy and safety of drugs in breast milk needs to be provided to the mother, with emphasis on the fact that sometimes data are sparse and the long-term effects on offspring are not known.

For the pregnant patient with active rheumatic disease, drug therapy is limited. There is a justifiable tendency to use as few drugs as possible during gestation; however, for many women, maintenance of treatment is necessary, and in a few women, disease activity will require aggressive management. Fortunately, low to moderate doses of corticosteroids are generally safe and

effective in most patients. Selected NSAIDs, hydroxychloroquine, sulfasalazine, and azathioprine may be considered for severe or life-threatening disease. There are also anecdotal reports of intravenous gamma globulin use⁸² and plasmapheresis⁹⁹ in pregnant patients with refractory antiphospholipid antibody syndrome or thrombocytopenia. When managing rheumatic disease in pregnant women, one must individualize therapy by carefully assessing and reassessing disease activity and severity, and by recognizing the risk to the fetus.

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