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INVITED LECTURE

RHEUMATOID ARTHRITIS AND PREGNANCY

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ABSTRACT

Rheumatologists often consider the dilemma about treating rheumatoid arthritis during pregnancy. Pregnancy alters the immune state, possibly contributing to a change in the course of RA. Disease activity was found to decrease during pregnancy but to increase after delivery. In about three fourths of pregnancies, the symptoms of the disease lessen. RA does not adversely affect pregnancy outcome. The RA monitoring during pregnancy include: identifying the activity of rheumatoid arthritis (RA), complications related to pregnancy, and adverse effects of the various medications. It is important to counsel patients about the teratogenicity and adverse effects of the medications used to treat rheumatoid arthritis (RA) before starting therapy. Patients may need a reminder about the importance of using contraception during DMARD therapy, especially methotrexate, leflunomide, and cyclophosphamide. Some of these medications may need to be discontinued several months before conception is planned (MTX at least 3 months before conception, leflunomide at least 2 years before conception). Women with RA who want to breastfeed are encouraged to do so. Careful planning, consulting with rheumatologist and gynecologist, adequate timing of the pregnancy and prenatal and postnatal care can result in pregnancy and motherhood which presents joy rather than difficulty for the patients with rheumatoid arthritis.

Key words: *rheumatoid arthritis, pregnancy, medications*

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic, chronic, autoimmune inflammatory disease, approximately 3 times more common in women than in men and often affects women during their reproductive years. Rheumatologists often consider the dilemma about treating rheumatoid arthritis during pregnancy. The most frequently discussed issue is the possible effect of the treatment on the fetal development and informing patients about the potential effect of pregnancy on disease. The influence of the rheumatic disease on pregnancy and vice-versa, as well as the influence of the disease and the treatment on women's fertility are also very important.

INCIDENCE AND CLINICAL DEVELOPMENT IN PREGNANCY

RA cases occur in about 1/1000 pregnancies to 1/2000 pregnancies. It is characterized by selective inflammation of the synovial with lymphocytic and monocytic infiltration.[1] Symmetrical joint involvement is typical. Extra-articular involvement includes vasculitis, lung disease, pericarditis, neuropathy, and subcutaneous

nodules.[2] The onset of this disease occurs with pain and swelling in one or more joints in the upper extremity. The progression of the disease then settles on the joints symmetrically, with the involvement of the lower extremities. Involvement of the distal finger joints is rare, and the spine is almost never involved. The hip joint may be affected, but this is usually a late manifestation of the disease. Pregnancy alters the immune state, possibly contributing to a change in the course of RA. Disease activity was found to decrease during pregnancy but to increase after delivery.[3] In about three fourths of pregnancies, the symptoms of the disease lessen. In these cases, most women experience relief in the first trimester that continues throughout the pregnancy. RA does not adversely affect pregnancy outcome. With occasional exception, RA returns after the third to fourth month postpartum.[2]

PATHOPHYSIOLOGY

The pathophysiology of the ameliorating effect of pregnancy on RA activity during pregnancy remains unknown, but various theories have been proposed. Nonetheless, no single mechanism satisfactorily explains the observed improvement, and multiple factors are probably responsible for the decreased disease severity. Some of the proposed theories are as follows:

1. The effect of pregnancy on cell-mediated immunity (eg, decreased cell-mediated immunity, predominance of helper T-cell 2 [TH2] cytokine profile)[4]
2. Elevated levels of anti-inflammatory cytokines, such as interleukin-1 receptor antagonist (IL-1Ra) and soluble tumor necrosis factor-alpha receptors (sTNFRs), and down-regulation of Th1 cytokines during pregnancy[5]
3. The effect of hormonal changes during pregnancy (eg, increased cortisol, estrogen, and progestin levels)[6]
4. The effect of pregnancy on humoral immunity (eg, a proportional decrease in immunoglobulin G lacking terminal galactose units, an elevated serum alpha-2 pregnancy-associated globulin [PAG] level)
5. Altered neutrophil function during pregnancy (eg, decreased neutrophil respiratory burst)[7]
6. The degree of HLA disparity between the mother and the fetus (the less genetically similar the mother and fetus, the more likely the RA will remit)

Possible causes for flare-ups during the postpartum period include the following:

1. A decrease in the anti-inflammatory steroid levels
2. Elevated levels of prolactin (ie, proinflammatory hormone)
3. Change in the neuroendocrine axis
4. Change from a TH2 to a helper T-cell 1 cytokine profile
5. Mortality/Morbidity

EFFECT OF RA ON PREGNANCY

A 2006 study suggests that RA during pregnancy does not affect the rate of spontaneous abortion.[8] The study showed an increased risk for prematurity but no increased risk for low birth weight after adjusting for gestational age.[9] RA does not appear to affect the likelihood of fertility; however, lower birth rates among women with RA have been reported. This may reflect choices by women to limit family sizes, as a recent study found that women diagnosed with RA prior to the birth of their first child had the fewest pregnancies and children.[10] The RA monitoring during pregnancy include: identifying the activity of rheumatoid arthritis (RA), complications related to pregnancy, and adverse effects of the various medications. Constitutional symptoms may be present. In most patients, morning stiffness and fatigue are diminished during pregnancy. Many patients notice improvement in joint pain or stiffness. Most patients who have a favorable response notice the decrease in pain as early as the first trimester and have durable relief throughout pregnancy. In some patients, this improvement occurs later, during the second or third trimester.[1] The study results show that 63% of patients experience relief but only 16% of patients achieve remission in the third trimester. The likelihood of developing extra-articular manifestations of RA during pregnancy is not increased. Nausea, vomiting, and morning sickness can occur during the first trimester. These symptoms may prevent absorption of medications. Pedal edema and back pain unrelated to RA can occur in the later stages of pregnancy.

PHYSICAL FINDING IN PREGNANCY

Pallor may be present. Patients with RA may have anemia of chronic disease. Pregnancy could further lower the hematocrit value following volume expansion. Joint examination is performed to assess disease activity. Activity is assessed based on the number of swollen tender joints. The pattern of the joint involvement in pregnant patients is the same as in the nonpregnant state (ie, involving small joints of the hands, wrists, shoulders, neck, knees, and ankles in a bilaterally symmetric pattern). Range of motion in the hip and neck joints is assessed to determine if the patient needs to abduct and externally rotate their hips for vaginal delivery and to identify patients with ligamental instability of the atlantoaxial joint. Assess for extra-articular

symptoms, including dry eyes, scleritis, dry mouth, pulmonary fibrosis, pleural effusion, and vasculitis is necessary. Because little available data suggest a significant risk for preterm birth, pre-eclampsia or fetal growth restriction in pregnant patients with RA, no special obstetric monitoring is indicated beyond what is performed for usual obstetric care.

PRECONCEPTION COUNSELING

It is important to counsel patients about the teratogenicity and adverse effects of the medications used to treat rheumatoid arthritis (RA) before starting therapy. Patients may need a reminder about the importance of using contraception during DMARD therapy, especially methotrexate, leflunomide, and cyclophosphamide. Some of these medications may need to be discontinued several months before conception is planned (MTX at least 3 months before conception, leflunomide at least 2 years before conception). In addition to discontinuation, some patients who take DMARDs may require treatment with other medications to enhance their clearance. Men who take azotropine should stop taking it three months before their partner try to conceive. NSAIDs should also be avoided in patients with fertility issues who are trying to become pregnant because of the risk that NSAIDs interfere with embryo implantation.

MEDICATION

The goals of pharmacotherapy are to reduce morbidity and to prevent complications. None of the medications used in the treatment of arthritis is absolutely safe during pregnancy. Hence, the decision to use medications should be made after careful assessment of the risks and benefits in consultation with the patient. Pain control through nonpharmacologic management (eg, paraffin baths, decreased physical activity, splinting, and cold packs) can be used as adjunctive care.

NSAID: NSAIDs should be stopped at the beginning of a menstrual cycle when conception is planned, as NSAIDs have been shown to interfere with blastocyst implantation in animal studies. Most traditional NSAIDs are considered Category B medications but should be used with caution in pregnancy.[11] Possible effects on the mother include prolonged gestation and labor, increased peripartum blood loss, and increased anemia. The potential adverse effects in the fetus include impaired fetal renal function with oligohydramnios and increased cutaneous and intracranial bleeding. Monitoring for oligohydramnios should be considered if the pregnant patient is on prolonged NSAID therapy. NSAIDs are contraindicated in the third trimester, as they promote premature closure of the ductus arteriosus, leading to fetal pulmonary hypertension. Ductal constriction can occur at any gestational age; however, one study noted a dramatic increase in indomethacin-induced ductal constriction at 31 weeks' gestation.[12] Stopping NSAID therapy prior to 31 weeks' gestational age is prudent for potentially avoiding adverse effects in the fetus. Short-acting NSAIDs (eg, ibuprofen, indomethacin, diclofenac) are preferred over long-acting agents.

Cyclooxygenase-2 (COX-2) inhibitors: Cyclooxygenase-2 (COX-2) inhibitors are generally considered Category C medications and potentially share the same side effects as traditional NSAIDs.

Corticosteroids:Corticosteroids are potent anti-inflammatory agents. They are considered relatively safe in pregnancy when used in low doses (ie, <20 mg) and are considered Category B medications. Nonetheless, they may increase the maternal risk of hypertension, edema, gestational diabetes, osteoporosis, premature rupture of membranes, and small-for-gestational-age babies. One meta-analysis found a 3.5-fold increase in risk of cleft palate in fetuses with first-trimester exposure to corticosteroids.[13] The choice of glucocorticoid depends on whether the mother or the fetus needs to be treated. Hydrocortisone and cortisone cross the placenta, but 11 beta-dehydrogenase, a placental enzyme, converts hydrocortisone to cortisone, which is biologically inactive; thus, the fetus is exposed to only approximately 10% of the maternal dose. Therefore, if steroid treatment is desired for the mother, hydrocortisone, cortisone, or prednisone should be chosen. Dexamethasone and betamethasone cross the placenta with similar maternal and fetal concentrations; thus, they are the treatment of choice for fetal respiratory distress. The lowest possible steroid dose needed to control activity should be used in pregnancy. Stress doses of steroids should be used during labor and delivery if the mother received steroids (even low-dose) for more than 2-3 weeks during pregnancy, and the neonate should be monitored for evidence of adrenal insufficiency and infection.

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS:

Methotrexat: Methotrexate, a folic acid antagonist, is contraindicated in pregnancy (Category X medication) because it is an abortifacient and has teratogenic effects, including craniofacial abnormalities, limb defects, and CNS defects such as anencephaly, hydrocephaly, and meningomyelopathy, especially with first-trimester exposure.[11] Because the active

metabolites have a long half-life, methotrexate must be discontinued at least 3 months prior to conception; treatment with folic acid should be continued in that period and throughout pregnancy.

Leflunomide: Leflunomide, a pyrimidine synthesis inhibitor, is also a Category X medication, and is extremely teratogenic and absolutely contraindicated in pregnancy. Its half-life is 14-15 days, but the active metabolite undergoes extensive enterohepatic circulation; thus, the drug takes up to 2 years to be undetectable in plasma. Therefore, discontinuation of the drug before conception is insufficient. The drug needs to be eliminated with administration of cholestyramine 8 g 3 times daily for 11 days. Plasma levels of less than 0.02 mg/L should be verified with 2 separate tests at least 2 weeks apart.[14] If unacceptably high levels persist, additional cholestyramine maybe given.

Sulfasalazine: Sulfasalazine, a dihydrofolate reductase inhibitor, is a Category B medication. Sulfasalazine does not increase fetal morbidity or mortality and is considered safe in pregnancy.[15]

Azathioprine: Azathioprine, although a Category D medication, can be used if the benefits outweigh the risks. Although fewer women who received azathioprine for renal transplantation completed their pregnancies, no increase in fetal anomalies was observed.[16] Azathioprine crosses the placenta, but the fetal liver lacks the enzyme inosinate pyrophosphorylase, which converts azathioprine to its active metabolite, 6-mercaptopurine; thus, the fetus is protected from the agent's teratogenic effects.[11] A retrospective cohort study of 155 patients found no statistical difference in conception failures, abortion secondary to a birth defect, major congenital malformations, neoplasia, or increased infections among patients taking 6-mercaptopurine compared with controls.[17] A study of 101 pregnancies of women with inflammatory bowel disease on azathioprine at doses of 100 mg/day revealed no association with poor pregnancy outcomes.[18]

Hydroxychloroquine: Hydroxychloroquine, an antimalarial agent, is considered a Category C medication. Previous reports of fetal toxicity with hydroxychloroquine were based on effects of chloroquine, which has 2.5 times the amount of tissue deposition as hydroxychloroquine.[19] No real fetal toxicity is associated with hydroxychloroquine at the dosage used for rheumatoid arthritis (RA) and connective-tissue disease (6.5 mg/kg body weight).[20] Several studies and case series have provided further evidence that no fetal toxicity was associated with hydroxychloroquine therapy in mothers. However, according to some other authors, antimalarials such as hydroxychloroquine should be avoided because they can cause fetal chorioretinitis.[21] Patients on the hydroxychloroquine must undergo ophthalmologic examination because of the possible drug toxicity.

Gold: Gold causes blood dyscrasias, drug rashes, and nephropathy and is therefore of theoretical risk to the fetus.[22]

BIOLOGIC AGENTS

Biologic agents are now commonly used for the treatment of RA; however, limited data are available on their use in pregnancy. Medications in the anti-TNF-alpha class (ie, currently, etanercept, adalimumab, and infliximab) are commonly used in the treatment of RA. They have been labeled by the FDA as Class B medications, as no adequate human studies have shown risk, but animal studies have shown no harm done to the fetus.[23] Thus far, no randomized, blinded, placebo-controlled trials have been completed to demonstrate any potential teratogenicity. Numerous case reports have showed positive outcomes with anti-TNF-alpha use in pregnancy, with an incidence of spontaneous abortion and birth defects similar to that in the general population.[24] Compared with healthy controls, the risk of preterm delivery and poor growth of offspring in all patients with RA is increased, but this is believed to be more attributable to the underlying systemic disease rather than to use of TNF blockers.

The Organization of Teratology and Information Specialist(OTIS) Project is the largest prospective cohort study to date evaluating anti-TNF-alpha medications and other medications used to treat autoimmune disease. This study, led by the University of California at San Diego, is maintaining a database of patients taking etanercept and adalimumab during first-trimester gestation.[25] The results for adalimumab have been updated and analyzed to May 2008. So far in this group there are 66 patients. Based on preliminary data, no concerns have been raised regarding the risks of adverse outcomes with adalimumab exposure, and rates of congenital defects are in range of the general population. As of October 2006, 48 pregnant patients had been enrolled and received treatment in the OTIS etanercept prospective cohort study. Based on preliminary data from this ongoing study, no concerns have been raised or consistent abnormalities found.[25] Because of the small sample size, no definitive conclusions about adalimumab or etanercept can be made at this time.

Rituximab: Rituximab, a monoclonal antibody that inhibits CD20 antigen on B lymphocytes, is currently a Pregnancy Category C medication. Rituximab is indicated for the treatment for moderate to severe RA. Case reports on the use of rituximab during pregnancy

have been reported in the oncology literature. Case reports have also shown that rituximab therapy results in detectable levels of the drug in cord blood and results in B-cell depletion in both mother and neonate.[26] Recovery of B-cell levels in the neonate has been reported to occur at age 3-4 months and does not appear to impair antibody formation to immunizations. The dosing of rituximab in case reports was 375 mg/m2 in 1-6 cycles.[27] Although it is unknown whether rituximab is excreted in human milk, IgG is present in human milk, and rituximab has been detected in the milk of monkeys.

Immunomodulators: Anakinra (Kineret), an interleukin-1 receptor antagonist, is used to treat severe RA. No studies or case reports using this medication during human pregnancy or lactation were found in the literature nor reported in data provided by the drug manufacturer. Anakinra is a Pregnancy Category B medication. No adverse effects have been reported in rats and rabbits receiving up to 100 times the recommended human dose.[28] No data are available to indicate whether anakinra is excreted in human milk.

Abatacept (Orencia) is a selective costimulation modulator that binds to CD80 and CD86, thereby inhibiting activation of T lymphocytes and interactions with CD.[28] Abatacept is indicated for the treatment of moderate to severe RA. No human studies have investigated the use of this medication during pregnancy or lactation. Similarly, no case reports have described abatacept therapy in human pregnancy or lactation in the literature or in drug company records. Abatacept, which is a Pregnancy Category C medication, has been found to cross the placenta and be excreted in rat milk. No teratogenic effects were reported in mice or rabbits treated with a dose 29 times greater than that recommended for humans.[29.]

Cyclosporine: There is insufficient information about the safety of cyclosporine during pregnancy. Most experts recommend that pregnant women take cyclosporine only if the potential benefits outweigh the potential risks.

BREASTFEEDING AND RHEUMATOID ARTHRITIS THERAPY

Approximately 90 percent of women with RA experience a flare during the postpartum period, usually within the first three months and particularly after a woman's first pregnancy. Many experts recommend restarting RA medications in the first few weeks after delivery. The postpartum period is a common time for women with RA to have a flare of the disease, so it is difficult to know if breastfeeding further increases this risk. However, there are numerous benefits of breastfeeding for both women and their infants. For these reasons, women with RA who want to breastfeed are encouraged to do so. Prednisone can be taken in low doses.

Azathioprine, cyclosporine, cyclophosphamide, methotrexate, and chlorambucil should be avoided during breastfeeding.

Diet: A low-fat, high-carbohydrate, high-fiber diet is recommended in pregnant patients with RA. Fish oils in moderate quantities can be taken during pregnancy. Calcium supplementation is recommended to prevent osteoporosis.

CONCLUSION

Rheumatoid arthritis usually has to be treated during pregnancy. Clinicians have to asses which medicine is safe and effective in the treatment of RA during pregnancy. Patients with RA can have as normal pregnancy as any other person. Careful planning, consulting with rheumatologist and gynecologist, adequate timing of the pregnancy and prenatal and postnatal care can result in pregnancy and motherhood which presents joy rather than difficulty for the patients with rheumatoid arthritis.

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