Managing Pregnancy in Rheumatic Disease Patients

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CHICAGO — The only “sure thing” about the medical management of pregnan
ty women who have a rheumatic dis-
 ease is that there are no sure things, ad-
vises a rheumatologist with particular
expertise in lupus.

“In an ideal world, pregnancy in these
women would always be planned; the
rheumatic disease would have been in re-
mis sion for at least 6 months at the time
of conception, and there would be a plan
for treatment if the disease flares. Unfor-
tunately, clinical medicine isn’t an ideal
world,” said Dr. Bonnie L. Bermas, direc-
tor of the Center for Lupus and An-
tiphospholipid Antibody at Brigham and
Women’s Hospital, Boston.

Exacerbating the challenge is the ab-
sence of any one-size-fits-all manage-
ment formula, Dr. Bermas said, noting
that the interplay among the individual
patient, disease, and treatment vari-
ables—all of which are unpredictable—
drives therapeutic decisions.

With rheumatoid arthritis (RA), for ex-
ample, “the literature supports that about
70%-80% of patients will go into remis sion
during pregnancy, though most will flare
post partum,” said Dr. Bermas at a sym-
posium sponsored by the American Col-
lege of Rheumatology (ACR). Even

though this knowledge provides clinicians
with some flexibility with respect to med-
ication during pregnancy, “we really can’t
predict who’s going to go into remis sion,
so we can’t say up front, ‘I guarantee
you’ll be able to go off treatment once you
become pregnant,’” she said.

Systemic lupus erythematosus (SLE),
on the other hand, is thought to be asso-
ciated with a slightly increased risk of
flare during pregnancy, said Dr. Bermas.
“This means that we will approach a lu-
pus patient differently than a rheumatoid
arthritis patient in terms of our manage-
ment plan, and the answers to the criti-
cal questions—‘Will the disease flare?
Will the baby be affected by the disease?
What medications are safe to take during
pregnancy?’—will be different.”

Although the Food and Drug Adminis-
tration’s use-in-pregnancy ratings for the
mainstays of rheumatic disease therapies
provide a management framework, there
is often a discrepancy between what the
FDA says is allowable during pregnancy
and what clinicians feel comfortable pre-
scribing, Dr. Bermas said.

NSAIDs, Cyclooxygenase-2 Inhibitors
Although animal studies have shown an in-
creased risk of congenital anomalies with
these agents, “when you get to the human
studies, there really is no increased risk of
congenital anomalies,” said Dr. Bermas.
“There is an increased risk of premature
closure of the ductus arteriosus in pa-

Drug Treatment
Considerations

The treatment of rheumatic dis-
 eases in pregnant women should
be based on disease severity and
drug safety, according to Dr. Bermas,
who suggested the following general
guide to treatment options:

Mild Disease
► For inflammatory arthritis, Dr.
Bermas recommends stopping drug
therapy before pregnancy or when
pregnancy is discovered.
► For SLE, maintain these patients
on hydroxychloroquine.
► NSAIDS are acceptable up to
week 24.

Moderate Disease
► Steroids should be used at the
lowest possible dose.
► Azathioprine should be used with
caut ion.
► Cyclosporin A should be used with
caut ion.
► Sulfasalazine should be used with
caut ion.

Severe Disease
► High-dose steroids should be used with
caut ion.
► Azathioprine should be used with
caut ion.
► Cyclosporin A should be used with
caut ion.
► Cyclophosphamide should be
used only in life-or-death situations.

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CARDIOVASCULAR AND OTHER RISKS Estrogens with or without progestins should not be used for
the prevention of cardiovascular disease or dementia. The Women’s Health Initiative (WHI) estrogen-alone
substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women
(50 to 79 years of age) during 6.8 years and 7.1 years, respectively, of treatment with daily oral conjugated
estrogen (CE 0.625 mg), relative to placebo.

The estrogen plus progestin WHI substudy reported increased risk of myocardial infarction, stroke, invasive
breast cancer, pulmonary embolus, and DVT in postmenopausal women (50 to 79 years of age) during 5.6 years
of treatment with daily oral CE 0.625 mg combined with medroxyprogesterone acetate (MPA 2.5 mg), relative
to placebo.
tients exposed to nonsteroids late in pregnancy, so we counsel patients that they can use nonsteroids up to 24 weeks’ gestation. We could probably protract this out to 30 weeks, but it’s easier to say, ‘stop the NSAIDS in the third trimester.’”

For patients trying to conceive, “we advise that they avoid using COX-2s and NSAIDs during the conception cycle because both can have an impact on implantation,” Dr. Bermas noted.

Antimalarials
A single case report of congenital defects in three of four babies born to one mother who took 250 mg of chloroquine two times a day during each of her four pregnancies earned antimalarials an FDA category C rating, “which is sort of representative of how the literature about medication in pregnancy has been interpreted over the years,” said Dr. Bermas. In the meantime, she said, there have been several case series in which no increased risk of congenital anomalies has been seen, and the literature on the use of these drugs as malarial prophylaxis (at higher doses than are used to treat rheumatic disease) has identified no untoward effects in pregnant women.

“For many years, we didn’t use any of these drugs during pregnancy, but a recent ACR survey showed that most rheumatologists today are comfortable leaving patients on antimalarials during pregnancy,” said Dr. Berman. “Having said that, if I have an RA patient whose main medication is hydroxychloroquine, that patient probably has fairly mild disease. Considering that most RA patients go into remission during pregnancy, I usually recommend stopping the drug during gestation.”

But for a patient with SLE who is well maintained on hydroxychloroquine, “I’d probably keep the medication on board,” because additional data show that patients with lupus who remain on therapy have better outcomes.

Steroids
For flares of most rheumatic diseases, steroids are considered “the ace in the hole,” said Dr. Bermas.

“During pregnancy, if rheumatoid arthritis, for example, becomes active, most clinicians recommend starting treatment with the lowest dose possible of a glucocorticoid medication, most commonly prednisone.” Both prednisone and methylprednisolone cross the placenta, but only at low levels, she said.

“The data on steroid safety during pregnancy are mixed. Originally, there were some case reports of cleft palate formation Continued on following page

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The Women’s Health Initiative Memory Study (WHIMS), a substudy of the WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE 0.625 mg alone and during 4 years of treatment with daily CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

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in offspring, although no increased risk of fetal anomalies was found in a large series of asthma patients treated with steroids throughout pregnancy," said Dr. Bermas. "In a meta-analysis of epidemiological studies, however, there was a 3.4-fold increase in the incidence of cleft palate formation associated with maternal exposure to corticosteroids (Teratology, 2000;62:385-92)," she said. "The key time frame seems to be between weeks 6 and 12, when the palate is forming."

Corticosteroids during pregnancy are also associated with maternal complications, including gestational diabetes, hypertension, and accelerated osteoporosis. "For this reason, the goal should always be to keep the dose as low as possible," she said.

Azathioprine and 6-Mercaptopurine

The use of azathioprine, a nonbiologic disease-modifying antirheumatic drug, is generally limited to women with severe disease who have not responded to other treatments, Dr. Bermas stated. There are conflicting data about the safety of this drug during pregnancy. Animal data suggest that the drug is teratogenic, and there have been case reports of fetal malformations, but transplant series indicate that the medication does not increase the rate of congenital anomalies, she said. Small-for-gestational-age babies and premature rupture of membranes are associated with use of the drug during pregnancy.

As with azathioprine, the nucleoside analog 6-mercaptopurine is teratogenic in animals, and it is plagued by conflicting human data. Some of the human studies suggest that there is an increased risk of congenital anomalies, but the gastrointestinal literature doesn’t support this," Dr. Bermas noted. "From a rheumatology perspective, this medication is rarely used, so I would suggest discontinuing it during pregnancy."

Sulfasalazine

"Case reports of fetal malformations linked to sulfasalazine from the inflammatory bowel disease literature didn’t pan out in our patient," Dr. Bermas. "This drug can be used in pregnancy. It does cause azooxia in men, however, so if you have a male patient who is interested in trying to get his partner pregnant, advise him to stop taking sulfasalazine for 3 months before conception for spermogenesis."

Penicillamine

Occasionally used in the treatment of progressive systemic sclerosis, penicillamine

Continued from previous page
has been shown to interfere with collagen biosynthesis and to cause malformations in animal studies, according to Dr. Bermas. “In humans, cases of cutis laxa and connective tissue disorders have been reported with exposure to this medication,” she said. As such, “this medication should be avoided during pregnancy,” she said.

**Mycophenolate Mofetil**

“We had such high hopes for mycophenolate mofetil. We thought this would be one of those medications that could be safely used during pregnancy,” said Dr. Bermas. “Unfortunately, there have been case reports of congenital anomalies, including one report of the drug being used during pregnancy in a renal transplant patient. The baby was born prematurely and was noted to have hypoplastic lungs, short fifth fingers, and congenital heart defects, including 8 patients with RA—who were diagnosed with inflammatory chronic diseases—in one large study comprising 131 patients (Br J Rheumatol, 2004;99:2385-92).

**Adverse Reactions**

Methotrexate can cause severe drug-induced ulceration. Patients with severe ulcerative colitis are at risk for toxemia and possible death. Methotrexate is known to cause a variety of side effects, including nausea, vomiting, and alopecia.

**Concomitant Use with Other Drugs**

Methotrexate can cause severe drug-induced ulceration. Patients with severe ulcerative colitis are at risk for toxemia and possible death. Methotrexate is known to cause a variety of side effects, including nausea, vomiting, and alopecia.

**References**


**Pregnancy**

**Evanism (estradiol transdermal spray)**

Evanism should not be used during pregnancy (see Contraindications). There appears to be no risk or increased risk of birth defects in those women who have used estradiol.