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Safety of Immunosuppressive Drugs in Pregnant Women with Systemic Inflammatory Diseases

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In the U.S., it is estimated that more than 4.5 million patients are affected by systemic inflammatory conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis, other inflammatory arthropathy, and inflammatory bowel disease (IBD). (1-3) These diseases often occur in women of childbearing ages. The safety of treatment for systemic inflammatory diseases during pregnancy is a major concern for both patients and their providers. For patients with no or minimal symptoms of systemic inflammatory diseases at conception, discontinuing immunosuppressive therapy before or right after conception might be an ideal option. Patients with active disease, however, need to continue immunosuppressive drugs to control the disease even during pregnancy as the disease activity seems to be an important predictor of pregnancy outcome across different systemic inflammatory diseases.(4-6)

What kind of questions would women with systemic inflammatory disease who are considering pregnancy or become pregnant ask with regard to their treatment options? They would ask whether to discontinue treatment during pregnancy, and what the risks are for the baby as well as for themselves if disease activity worsens. If treatment is indicated, they would also ask which immunosuppressive drug to use, given the possibility of early fetal exposure to the medication. In other words, the equation that affects treatment decision making for these patients include benefits and risks of immunosuppressive drugs in the mother and offspring.

What do we know about the safety of these immunosuppressive drugs in pregnancy? Unfortunately, only limited information is available with respect to the comparative safety of immunosuppressive agents in pregnancy. Many immunosuppressive drugs used in patients with systemic inflammatory disease are absolutely or relatively contraindicated during pregnancy because of their teratogenic potential (see Table 1 for the U.S. Food and Drug Administration (FDA) pregnancy). Among many non-biologic immunosuppressive drugs, hydroxychloroquine and cyclosporine are considered relatively 'safe' to use in

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pregnancy. Hydroxychloroquine can cross the placenta, but appears to have no effects on congenital defects, fetal death, or prematurity.(7-9) Safety data on use of cyclosporine in pregnancy from transplant patients suggest a possible risk of preterm birth and low birth weight but no congenital defects.(10) Thiopurines, azathioprine or mercaptopurine, are thought to be safe in pregnancy due to the inability of the fetus to metabolize these drugs to their active metabolites.(11, 12) *In utero* exposure to mycophenolate has been associated with a higher incidence of structural birth defects such as microtia, cleft lip, and other anomalies.(13, 14) Methotrexate is known to have embryotoxic and teratogenic effects and is also used as an arbotifacient. As the toxicity of methotrexate seems to be dose-dependent, some studies have questioned the fetal toxicity of low-dose methotrexate commonly used in patients with rheumatic conditions.(15) Leflunomide is also embryotoxic and teratogenic and has a long duration of action, but the Organization of Teratology Information Specialists research group did not find an increased risk of adverse pregnancy outcomes due to leflunomide use among women who underwent cholestyramine wash-out early in pregnancy.(16, 17)

Short-term and long-term pregnancy safety data on TNFi is limited although a number of studies did not find a significant risk of adverse pregnancy outcomes in pregnant women exposed to TNFi.(11, 18-20) The preliminary results from the Pregnancy in IBD and Neonatal Outcomes (PIANO) study showed a no significant risk of congenital anomalies but a 1.5 times increased risk of neonatal infection related to use of both TNFi and thiopurines compared to untreated women during pregnancy.(21)

The study by Cooper and colleagues(22) in this issue of *Arthritis and Rheumatism* investigated the risk of congenital malformations, fetal deaths, and serious neonatal complications in women exposed to immunosuppressive drugs for systemic inflammatory conditions during pregnancy. Using claims data from 3 U.S. health plans linked to vital records as well as medical records, they identified 608 pregnancies in 573 women with a wide range of immune-mediated diseases. Of those, 402 pregnancies were exposed to immunosuppressive drugs within the 1st trimester, 35 within the 2nd or 3rd trimester, and 171 had no use of immunosuppressive drugs during pregnancy. 4.1% of all pregnancies had major congenital malformations and 1.6% had fetal deaths. Compared to pregnancies unexposed to immunosuppressive drugs, the propensity score-adjusted risk ratio for congenital malformation was elevated across 4 different immunosuppressive drug groups, ranging from 1.42 in other immunosuppressive drugs to 3.11 in hydroxychloroquine, with wide confidence intervals. Fetal deaths occurred most frequently among women exposed to methotrexate in the 1st trimester (8.7%) with propensity score-adjusted risk of 3.18 (95% confidence interval (CI) 0.54-18.62). Life-threatening neonatal complications occurred in a total of 33 (5.4%) pregnancies. Among the term births, the propensity score-adjusted risk ratio for life-threatening neonatal complication was again the highest in the methotrexate group (5.9, 95% CI 0.34-103.86). The authors concluded that there was no significant increase in fetal risks in pregnancies with the 1st trimester exposures to methotrexate, hydroxychloroquine, TNFi, and other immunosuppressive drugs.

Assessment of the comparative safety of therapeutic alternatives (including no treatment) of a systemic inflammatory condition during pregnancy is challenged by the relatively small

number of women with these conditions exposed to specific drugs during pregnancy. Despite the large source population-based of over 8 million subjects from 3 different health plans, the Cooper *et al* study was still limited by insufficient statistical power to evaluate the risk of specific drugs in relation to specific outcomes. Let us suppose there are 1,000 patients exposed to a specific immunosuppressive drug or category of interest and there are 5,000 unexposed patients as a comparator. Approximately 3% of babies are born with a birth defect in the U.S.(23) The power to detect a significant difference in the risk of any birth defect with α=0.05 (2-sided) would be 0.67 for an expected relative risk of 1.5 and 0.99 for an expected relative risk of 2.0. If there are only 100 exposed and 500 unexposed patients, the power would be 0.15 for an expected relative risk of 1.5 and 0.35 for an expected relative risk of 2.0. Not surprisingly, it is much more difficult to conduct a study with an adequate power for a specific malformation as the proportion of babies with a specific malformation is even lower in the source population and ranges from 0.008% for encephalocele to 0.1% for oral cleft.

The authors confronted the challenge with an innovative approach in perinatal pharmacoepidemiology: Like many randomized trials do in non-pregnant populations, the authors used a composite outcome and considered all fetal outcomes combined. While not ideal, this approach circumvents the small sample size problem with a more clinically informative compromise than the alternative, i.e., combining specific drugs. From a biological point of view, we would still need to know whether any of the studied drugs causes specific fetal problems. For example, the lack of significant associations could be due to a reduced risk of some adverse fetal outcomes with continuation of medications in women with specific systemic inflammatory diseases, balanced out by an increased risk of other fetal outcomes caused by these medications. If that were the case, the overall risk of adverse fetal outcomes would be higher than in the general population but similar among continuers and discontinuers of treatments among women with systemic inflammatory diseases. However, for patients and health care providers, these findings on the overall fetal safety adds relevant data to the previously scarce evidence we had to inform treatment decisions in pregnant women with systemic inflammatory diseases.

For confounding control, Cooper *et al* compared women with systemic inflammatory disease who used immunosuppressive drugs during pregnancy to women with systemic inflammatory disease who used immunosuppressive drugs prior to conception. In addition, the authors calculated a propensity score, which is a probability of using immunosuppressive drugs versus not using such drugs based on sociodemographic factors, comorbidities, medications, types of systemic inflammatory disease, geographic region, and calendar year. However, the role of disease activity or severity on fetal risks was not controlled for.

Going back to clinical questions being asked by women considering pregnancy who have systemic inflammatory diseases, we still have many unanswered questions. Balancing the maternal and fetal risk and the benefit of immunosuppressive therapy is the key in management of systemic inflammatory diseases during pregnancy. The overall benefits of immunosuppressive drugs in patients with systemic inflammatory diseases are well-known, although the benefits of immunosuppressive drugs specific to pregnancy outcomes have not been well studied. For the risk of major congenital malformations related to newer

immunosuppressive drugs, some reassuring, albeit not definitive, data on TNFi from the results of Cooper *et al* and other previous reports is available.(21, 22) The effect of other biologic agents on fetal risks, however, remains uncertain. Comparative safety of immunosuppressive drugs on short- and long-term outcomes in mothers as well as offspring should be also studied.

Due to feasibility and ethical issues, conducting randomized controlled trials that can answer questions about drug safety in pregnancy is not possible. Second best might be a large-scale population-based cohort of women with systemic inflammatory disease that contains prospectively collected data on sociodemographic factors, obstetric history, use of medications including immunosuppressive drugs, comorbidities, disease activity markers, and various health outcomes in both mothers and offspring. We have a long way to go before we can provide evidence-based guidance on management of women with various systemic inflammatory diseases who plan to become pregnant or in women who unexpectedly become pregnant while receiving immunosuppressive treatment. With the appropriate epidemiologic and statistical methodology, big linked datasets, including health care claims, electronic medical records, and other registries, may facilitate obtaining relevant information for this important question.

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Table 1

US Food and Drug Administration pregnancy category of immunosuppressive drugs for systemic inflammatory diseases

	Description	Non-biologic immunosuppressive Drugs	Biologic immunosuppressive drugs
A	Adequate and well-controlled human studies fail to show a fetal risk	None	None
B	Animal studies fail to show a fetal risks and there are no human studies	Sulfasalazine, mesalamine[A]	Adalimumab, alefacept, anakinra, certolizumab, etanercept, golimumab, infliximab, ustekinumab
C	Animal studies show a fetal risk and there are no adequate human studies	Cyclosporine, gold, hydroxychloroquine[b], tacrolimus	Abatacept, natalizumab, rituximab, tocilizumab
D	There is evidence of fetal risk, but the benefits may outweigh the risks	Azathioprine, cyclophosphamide, D-penicillamine, mercaptopurine, mycophenolate	
X	There is evidence of fetal risk and the risks clearly outweigh any possible benefits	Leflunomide, Methotrexate	

[A] sacol is in category C,

[b] not officially classified