

SPECIFIC CHARACTERISTICS AND DIFFERENCES OF THE IMMUNE STATUS OF PREGNANT AND LACTATING WOMEN

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ABSTRACT

This article describes the peculiarities of the immune status of pregnant and lactating women. Their different aspects are compared. The use of drugs that enhance the immune status of pregnant and lactating women. Their positive and negative aspects are discussed.

Key words: *immune status, pregnant and lactating women, immunomodulating drugs.*

ОСОБЕННОСТИ И РАЗЛИЧИЯ ИММУННОГО СТАТУСА БЕРЕМЕННЫХ И КОРМЯЩИХ ЖЕНЩИН

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АННОТАЦИЯ

В данной статье описаны особенности иммунного статуса беременных и кормящих женщин. Сравниваются их различные аспекты. Применение препаратов, повышающих иммунный статус беременных и кормящих женщин. Обсуждаются их положительные и отрицательные стороны.

Ключевые слова: *иммунный статус, беременные и кормящие женщины, иммуномодулирующие препараты.*

INTRODUCTION

In the Uzbekistan alone, there are approximately 0.25 million people affected by autoimmune diseases such as systematic lupus erythematosus, rheumatoid arthritis, and inflammatory bowel disease . Once considered chronically debilitating, these disorders can now be managed successfully using a variety of immunomodulating drugs, defined in this document as agents that inhibit or modulate the immune response. Because autoimmune conditions occur more often among women of childbearing age , continuation of these medications during pregnancy is

often considered to optimize disease management in the woman and pregnancy outcomes, without placing the fetus at undue risk. Emerging safety and efficacy data regarding the use of these medications during pregnancy and lactation can be used to counsel women with autoimmune disease who are pregnant or contemplating pregnancy.

Because autoimmune conditions occur more often among women of childbearing age, continuation of these medications during pregnancy is often considered to optimize disease management in the woman and pregnancy outcomes, without placing the fetus at undue risk. Many commonly prescribed drugs can be used safely during pregnancy, without risk of teratogenicity or pregnancy complications, whereas a few are strictly contraindicated. The decision to use any agent during pregnancy should be based on the clinical context, risks associated with individual medications, and gestational age. For immunomodulators considered appropriate to use during pregnancy, the common clinical practice of stopping use at approximately 32 weeks of gestation because of theoretic concerns regarding the immune system of the fetus is not supported by currently available data. Low-risk medications typically are continued in pregnancy, or initiated during pregnancy as needed, because the benefits of therapy and disease control far outweigh any theoretic risks associated with the medication. Use or initiation of medications with intermediate risk or little or no data during pregnancy or lactation (or both) should be individualized. High-risk medications are typically not continued or initiated in pregnancy. However, it is critical that counseling occur, ideally in the prepregnancy and interpregnancy periods, to review the individual risks and benefits as they relate to disease management and pregnancy-associated risks with high-risk medication. There may be select circumstances when continued treatment is the safest option. In general, immunomodulating drugs that are not contraindicated in pregnancy are compatible with breastfeeding.

Prepregnancy Considerations: Congenital Malformations and Pregnancy Complications

Many commonly prescribed drugs can be used safely during pregnancy, without risk of teratogenicity or pregnancy complications, whereas a few are strictly contraindicated. Still others have not been sufficiently studied during pregnancy. The decision to use any agent during pregnancy should be based on the clinical context, risks associated with individual medications, and gestational age. In addition, counseling should include the prepregnancy and interpregnancy periods for treatment planning because many of these medications have long half-lives.

In general, these medications can be considered in four categories: 1) low risk in pregnancy, 2) low risk emerging therapies with developing evidence for use during

pregnancy, 3) intermediate risk with little or no existing data on use in pregnancy, and 4) high-risk medications generally contraindicated in pregnancy. For immunomodulators considered appropriate to use during pregnancy, the common clinical practice of stopping use at approximately 32 weeks of gestation because of theoretic concerns regarding the immune system of the fetus is not supported by currently available data.

Low-risk medications typically are continued in pregnancy, or initiated during pregnancy as needed, because the benefits of therapy and disease control far outweigh any theoretic risks associated with the medication.

Glucocorticoids

Glucocorticoid preparations are commonly given during pregnancy, both as maintenance therapy and in short “bursts” to treat disease exacerbation. Oral corticosteroids, such as prednisone, prednisolone, or methylprednisolone, are recommended during pregnancy because of their conversion to relatively inactive forms by the abundance of 11 β -hydroxysteroid dehydrogenase found in the human placenta. Long-term glucocorticoid treatment during pregnancy may increase the risk of hypertension, preeclampsia, weight gain, hyperglycemia, immunosuppression, gastrointestinal ulceration, prelabor rupture of membranes (also referred to as premature rupture of membranes), and intrauterine growth restriction, but if these risks exist the magnitude is not known. Early data suggested that first trimester exposure to glucocorticoids may be associated with an increased risk of fetal oral clefts, but more recent data have failed to demonstrate an association.

Aminosalicylates

Sulfasalazine, a combination of salicylate and a sulfa antibiotic, is used most commonly during pregnancy to treat inflammatory bowel disease. Although both sulfasalazine and its metabolite, sulfapyridine, cross the placenta, teratogenic effects have not been demonstrated. Sulfasalazine inhibits dihydrofolate reductase. Whether the addition of folic acid supplementation is important among women taking sulfasalazine is not known and is not part of any current clinical recommendations.

Azathioprine

Azathioprine is a derivative of mercaptopurine, which blocks DNA replication and inhibits purine synthesis. Azathioprine is used to treat several autoimmune conditions and recipients of organ or tissue transplants. Existing data do not demonstrate azathioprine is a teratogen, although a few reports suggest an increased risk of preterm birth and fetal growth restriction when azathioprine is continued during pregnancy.

Cyclosporine A

Cyclosporine A works by inhibition of production and release of interleukin II

and inhibition of interleukin II activation of resting T lymphocytes. Limited data suggest no teratogenic effect of cyclosporine A use during pregnancy, although increased risks of preterm birth and growth restriction have been reported. Ophthalmic cyclosporine A does not produce detectable amounts of drug in the serum and is not expected to confer any fetal risk.

Hydroxychloroquine

Hydroxychloroquine is an antimalarial drug with antiinflammatory effects and often is used for maintenance therapy for autoimmune conditions. Although its mechanism of action is unclear, multiple studies have demonstrated no evidence of teratogenicity. Importantly, hydroxychloroquine may be more effective than glucocorticoids in disease flare prevention during pregnancy and should be continued in patients using this therapy.

Low-Risk Emerging Therapies with Developing Evidence

Newer classes of immunomodulating medications are being used in clinical practice because of their highly effective disease-modifying effects. The data regarding safety of these medications are emerging, but currently available data would suggest that they are low risk to continue or initiate in pregnancy.

Tumor Necrosis Factor- α Inhibitors

Several tumor necrosis factor- α (TNF- α) inhibitor drugs are currently used as maintenance medications for autoimmune disease, including infliximab, etanercept, adalimumab, certolizumab, and golimumab. Inhibition of TNF- α results in an increase in circulating T regulatory cells and a restored capacity to inhibit cytokine production. With the exception of certolizumab, all TNF- α inhibitors are transferred across the placenta. Placental transfer of certolizumab does not occur because it lacks an Fc portion required for active transport.

Initial reports of an association between TNF- α inhibitors and fetal VACTERL (Vertebral anomalies, Anal atresia, Cardiac defects, Tracheoesophageal fistula, Esophageal atresia, Renal anomalies, and Limb dysplasia) syndrome have not been confirmed in subsequent large observational trial.

No relationship between preterm birth and TNF- α inhibitor use during pregnancy was identified in one retrospective, multicenter cohort study of women with inflammatory bowel disease that compared pregnancy outcomes in 318 untreated patients, 187 patients taking azathioprine, and 66 patients taking TNF- α inhibitors (adjusted odds ratio [aOR], 1.6; 95% CI, 0.9–2.8). Azathioprine exposure appeared to be protective when outcomes were compared between treated and untreated women (aOR, 0.6; 95% CI, 0.4–0.9). In contrast, the risk of preterm birth was found to be higher in a prospective observational cohort study of women exposed to one of five available TNF- α inhibitors during at least the first trimester (aOR, 1.6;

95% CI, 1.1–2.5).

Medications with Indeterminate-Risk or Little or No Data

Use or initiation of medications with intermediate risk or little or no data during pregnancy or lactation (or both) should be individualized. Active maternal disease often presents the greatest risk, and the small known or theoretic risks of a medication are outweighed by the need for treatment.

Cyclophosphamide

Cyclophosphamide is converted by the liver into phosphoramide mustard, which is an alkylating agent that inactivates DNA. Cyclophosphamide also has anti-inflammatory effects on the B lymphocytes and T lymphocytes. Older data in animals and humans suggested that use in the first trimester should be avoided because of possible teratogenic effects. No adverse effects of cyclophosphamide use during the second and third trimesters have been reported in observational studies.

Rituximab

Rituximab is a humanized monoclonal antibody targeted at CD20 antigen on B lymphocytes. Safety data of use during pregnancy and the 6 months before pregnancy are limited, although published reports are reassuring. Safety of rituximab during lactation has not been studied.

Belimumab

Belimumab is an inhibitor of B lymphocyte survival as well as B cell conversion to immunoglobulin secreting cells. A single case report of use during pregnancy describes good disease control of systemic lupus erythematosus but mild Epstein's anomaly in the infant. It is unclear if belimumab is a teratogen based on this case report. Use of belimumab in pregnancy and lactation remains otherwise unstudied.

High-Risk Medications

High-risk medications are typically not continued or initiated in pregnancy. However, it is critical that counseling occur, ideally in the prepregnancy and interpregnancy periods, to review the individual risks and benefits as they relate to disease management and pregnancy-associated risks with high-risk medication. There may be select circumstances when continued treatment is the safest option.

Methotrexate

Methotrexate is commonly used to provide long-term, maintenance immunosuppression in patients with autoimmune conditions. However, its use during pregnancy is strictly contraindicated because methotrexate has abortogenic and teratogenic effects. Although there are not published reports of methotrexate-related birth defects when pregnancy is not delayed, expert opinion suggests that women delay pregnancy for 1–3 months after discontinuation of methotrexate because

methotrexate may persist for up to 4 months in the liver.

Mycophenolate

Mycophenolate is frequently used as maintenance therapy in patients with lupus nephritis. It works by inhibition of purine biosynthesis. Like methotrexate, mycophenolate is abortogenic and teratogenic, having been associated with cleft lip and palate, micrognathia, microtia, and auditory canal abnormalities. Expert opinion suggests pregnancy should be delayed 6 weeks after discontinuing mycophenolate.

Leflunomide

Leflunomide works by inhibition of dihydroorotate dehydrogenase, an enzyme necessary for pyrimidine biosynthesis. It is routinely used to treat inflammatory arthritis and lupus-related skin manifestations. However, it should not be used during pregnancy because of its teratogenic effects, after reports of associated facial malformations. The metabolite of leflunomide (teriflunomide) remains detectable as long as 2 years after drug discontinuation.

Breastfeeding and Infant Considerations

The amount of medication transmitted into breast milk and the potential effect on the neonate are important considerations when the use of immunomodulating drugs is being considered for women who are lactating. In general, immunomodulating drugs that are not contraindicated in pregnancy are compatible with breastfeeding. A multicenter prospective cohort study of breastfeeding women who received immunomodulating therapies for inflammatory bowel disease demonstrated low drug concentrations in breast milk and no evidence of increased risk of infection or adverse neurodevelopment in the infant. Although some expert opinions recommend limiting exposure to these medications during lactation, data to support that practice are limited. Given the evolving information on these medications, health care providers are encouraged to use LactMed to find the most up-to-date information for counseling.

Evidence for Presence in Breast Milk

Data describing the amount of immunomodulators that are detectable in breast milk are limited to small series and case reports. Based on what is known about pharmacokinetics and breast milk, it is unlikely that these medications are present at any significant level in breast milk, if they are detectable at all. This was demonstrated in a recent prospective multicenter study, with very low drug levels of biologic medications detected in breast milk. Tumor necrosis factor- α inhibitors are also large molecules, which are likely to be broken down by the infant's gastrointestinal tract.

Infant Effects

There has been concern that infants born to women who received

immunomodulating therapies during pregnancy or while breastfeeding might have their immune systems negatively affected. A recent prospective study of 80 women taking TNF- α inhibitors during pregnancy, with or without thiopurines found that the drug was detectable until 12 months of age in some infants. The authors also found an increased risk of infection among the infants born to women who used both therapies (relative risk [RR], 2.7; 95% CI, 1.09–6.78). However, when comparing risk of infection between women taking TNF- α inhibitor monotherapy who discontinued the medication at 30 weeks of gestation with those who did not discontinue the medication, no difference was seen (RR, 0.54; 95% CI, 0.26–1.16). Therefore, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend that women do not discontinue these medications during pregnancy or breastfeeding.

The effects of immunomodulating drugs on neonatal immunity were evaluated in a prospective study that used a U.S. registry database to identify women treated for inflammatory bowel disease with a variety of agents during pregnancy. No differences in antibody levels to *Haemophilus influenzae* or tetanus toxin were identified in serum collected at age 7 months from exposed and unexposed neonates. In another study of 841 children with a 4-year mean follow-up, children born to women with in utero TNF- α inhibitor exposure were no more likely to experience severe infections than their unexposed peers. A single report on women exposed to rituximab described B-cell lymphocytopenia in the neonates months after birth. This finding has not been confirmed by other studies.

Future Research for Pregnant Women

The established efficacy of immunologic therapies in pregnant women has led to their widespread use, which makes counseling challenging for the obstetric care provider given the paucity of existing data. It is important that pregnant and lactating women be enrolled in studies and registries to support a larger body of literature to guide evidence-based obstetric practice.

CONCLUSION

Immunomodulating drugs are being used with increasing frequency for a variety of diseases because of their demonstrated efficacy. Many commonly prescribed drugs can be used safely during pregnancy without risk of teratogenicity or pregnancy complications, whereas a few are strictly contraindicated. Importantly, decision making regarding patient plans should be individualized and shared and should include consideration of pregnancy and maternal risks associated with untreated disease. Finally, the body of literature to support evidence-based use of immunomodulating agents in pregnant and lactating women is very limited, and future studies are expected to help inform ongoing clinical guidance.

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