### Update on biologic safety for patients with psoriasis during pregnancy

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Review

Update on biologic safety for patients with psoriasis during pregnancy

Martina L. Portera, Stephen J. Lockwood, Alexa B. Kimball

Abstract

Biologic agents have become more common to treat patients with psoriasis, but concerns about their effect on pregnancy and lactation often preclude this treatment during these time periods. During the past decade, we have gained a much better understanding of the course of psoriasis during pregnancy and the safety of the use of biologic agents during pregnancy and lactation. Under certain circumstances, biologic agents can be considered appropriate treatment options for patients who are pregnant or lactating.

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Introduction

Psoriasis is a chronic, immune-mediated inflammatory disorder. Psoriasis prevalence rates are estimated between 1.5% and 2% worldwide, and more than 7.2 million people are affected in the United States alone (Jacobson et al., 2011; Rachakonda et al., 2014). The average age of female patients at the time of disease onset is 28 years, which means that many of these patients with psoriasis are of childbearing potential (Tauscher et al., 2002).

Over the past decade, we have seen the emergence of biologic agents as a mainstay of treatment for patients with psoriasis. In 2013, approximately 25% of patients with psoriasis were treated with biologic agents and primarily with tumor necrosis factor-alpha (TNF-alpha) inhibitors such as adalimumab and etanercept (Armstrong et al., 2013). Today, newer and even more effective biologic therapies with more targeted mechanisms of action are available to patients. Thus, it is expected that most dermatologists will encounter female patients with psoriasis who are pregnant or desire to become pregnant while treated with a biologic agent. Data on this subject are limited but expanding, and dermatologists who have an understanding of the clinical course of psoriasis and the impact of biologic agents during pregnancy will be better equipped to weigh the risks and benefits of treatment and counsel patients appropriately.

Psoriasis and pregnancy

Pregnancy is marked by complex maternal hormonal and immune system changes. During pregnancy, the maternal immune system shifts from a T helper (Th) cell 1 to a Th2 response. With this shift, certain Th2-mediated diseases such as lupus erythematosus worsen during pregnancy (Ruiz et al., 2014). Other T cell subsets that are related to autoimmune diseases include Th17 and T regulatory (Treg) cells. A recent review article found a greater ratio of Th17 to Treg cells in patients with pregnancy complications and autoimmune diseases and a reversal of this ratio in patients who had a successful pregnancy with a tolerance to self-antigens (Figueiredo and Schumacher, 2016).

Psoriasis is thought to be a primarily Th17-mediated disease with some Th1 involvement and since both of these cells are downregulated during pregnancy, a patient’s disease status can ameliorate during pregnancy. Psoriasis tends to improve for approximately half of patients, but an equal number of patients report no change or worsening of their psoriasis during pregnancy (Bobotsis et al., 2016; Murase et al., 2005). Additionally, the majority of patients with psoriasis report immediate postpartum disease flares (Murase et al., 2005).

Psoriasis comorbidities such as diabetes, metabolic syndrome, cardiovascular disease, and depression may also increase the risk of negative birth outcomes. A prospective cohort study of pregnant women with psoriasis compared with pregnant women who had no autoimmune disease found that patients with psoriasis were...
more likely to smoke during the first trimester of pregnancy, be overweight or obese, and have a diagnosis of depression. These patients were also less likely to use prenatal vitamins or folic acid supplementation at the time of conception, and such modifiable risk factors could increase the risk for adverse birth outcomes (Bandoli et al., 2010).

Pregnancy outcomes are generally poorer in patients with psoriasis. One study that was presented in 2012 at the European Academy of Dermatology and Venereology found that women aged 35 years and older with psoriasis had significantly lower pregnancy rates and live birth rates compared with disease-free control patients (Powers, 2012). Studies that analyzed pregnancy in patients with psoriasis have presented conflicting data with regard to poor pregnancy outcomes such as preterm birth, low birth weight, recurrent miscarriage, and increased cesarean delivery, with some studies supporting and others refuting these findings (Ben-David et al., 2008; Lima et al., 2012; Yang et al., 2011). However, a recent review of psoriasis and adverse pregnancy outcomes concluded that more recent literature suggested a link between psoriasis disease severity, pregnancy, and the development of adverse outcomes. The authors postulated that immune system dysregulation in psoriasis likely leads to poorer outcomes in pregnancy (Bobotsis et al., 2016).

**Fetal exposure to biologic agents during pregnancy**

Exposure of the fetus to biologic agents during pregnancy depends on the transport across the placenta. Immunoglobulin G (IgG) is the only major class of antibody that is transported across the human placenta. Fetal levels of IgG in umbilical venous blood are low in the first two trimesters of pregnancy and do not surpass maternal levels of IgG until the beginning of the third trimester when active transport of the IgG molecules across the placenta increases rapidly (Chambers and Johnson, 2012). Transport of IgG is facilitated by the neonatal Fc receptor (FcRn) on the placenta. Of the four subclasses of IgG (G1-G4), IgG1 is the most effectively transported followed by IgG4, IgG3, and IgG2, respectively (Wakefield et al., 2011). Adalimumab and infliximab are both IgG1 immunoglobulins. A prospective study of 80 patients with inflammatory bowel disease (IBD) who were treated with adalimumab and infliximab found an inverse correlation between time of last exposure to drug during pregnancy and umbilical drug concentrations in the infant (Julsgaard et al., 2016). Tranecetrapib is a fusion protein that also contains an IgG1 Fc portion but with less transplacental transport (Wakefield et al., 2011). Adalimumab and infliximab are both IgG1 immunoglobulins. A prospective study of 80 patients with inflammatory bowel disease (IBD) who were treated with adalimumab and infliximab found an inverse correlation between time of last exposure to drug during pregnancy and umbilical drug concentrations in the infant (Julsgaard et al., 2016). Tranecetrapib is a fusion protein that also contains an IgG1 Fc portion but with less transplacental transport than adalimumab or infliximab (Kurizky et al., 2015).

Certolizumab differs from other biologic agents because it is a pegylated antigen-binding fragment (Fab) antibody that lacks an Fc region. Without this Fc region, it cannot be actively transported by the FcRn receptor on the placenta and thus, results in minimal placental transmission (Wakefield et al., 2011). A case series of 13 patients with rheumatic disease who were treated with certolizumab during late pregnancy showed measurements of certolizumab in the cord blood between undetectable and 1 μg/ml compared with average maternal plasma levels of approximately 33 μg/ml (Föger et al., 2016). This suggests that certolizumab may be used as a treatment during late gestation without potential exposure to the newborn. Of note, certolizumab is only approved by the U.S. Food and Drug Administration (FDA) for the treatment of psoriatic arthritis but results from randomized, controlled Phase II studies have shown very good efficacy in patients with psoriasis (Reich et al., 2012).

This information is clinically significant for both the mother and fetus. Ideally, patients would discontinue treatment with biologic medications prior to planned pregnancies but for many patients with psoriasis, this situation is impractical and may not be necessary (Horn et al., 2009). Because of the minimal placental transport of maternal antibodies during the first two trimesters of pregnancy, treatment of patients with anti-tumor necrosis factor (TNF) alpha biologic medications is generally considered safe during the first half of pregnancy (Föger and Villiger, 2016). Recommendations for the use of anti-TNF therapy in the treatment of patients with IBD endorse discontinuation of TNF-alpha inhibitors at week 22-24 of pregnancy, but the rheumatology literature suggests safely continuing therapy up until Week 30 of pregnancy (Levy et al., 2016; van der Woude and Kanis, 2016). Newer consensus statements from the Canadian Association of Gastroenterology that were published in March 2016 state that women with a low-risk of IBD relapse and a compelling reason to discontinue treatment with anti-TNF therapy should stop at Weeks 22 to 24 but all other women with IBD who are treated with anti-TNF therapy are recommended to continue anti-TNF treatment throughout the pregnancy (Nguyen et al., 2016). These recommendations were classified as a “strong recommendation” on the basis of low-quality evidence but the assumption was that the risks of treatment with anti-TNF therapy outweighed the risk of an IBD relapse with subsequent effects on both the mother and fetus during pregnancy.

Patients with psoriasis who continue treatment with biologic agents during their pregnancy and particularly into the third trimester should be informed of the potential for an impaired immune response in their newborn infants. One case report of a death due to disseminated Bacillus Calmette-Guérin (BCG) infection following live BCG vaccination in an infant borne to a mother receiving infliximab during pregnancy, caused significant and warranted alarm (Cheent et al., 2010). Multiple studies have documented that levels of anti-TNF agents are detected in infants at birth and decline thereafter (Chambers and Johnson, 2012); however, a few studies noted that drug clearance could take up to 1 year after birth (Julsgaard et al., 2016). Infliximab clears more slowly than adalimumab (Julsgaard et al., 2016). Therefore, the administration of live vaccinations should be avoided in newborns with exposure to TNF-alpha agents for at least 6 months after delivery but inactive vaccinations can follow the standard schedule as recommended by the Centers for Disease Control and Prevention (CDC).

**General safety of biologic agents during pregnancy**

Most of the data on biologic agents and pregnancy come from the gastroenterology and rheumatology literature because TNF-alpha inhibitors are most commonly used to treat patients with IBD and rheumatoid arthritis. Because pregnant women are commonly excluded from clinical trials, large, controlled studies of TNF-alpha inhibitors and newer biologic agents, such as ustekinumab (IL-12/23 inhibitor), secukinumab (IL-17 inhibitor), and ixekizumab (IL-17 inhibitor), are lacking. Most of our limited observations come from data from animals, case reports or case series, small retrospective studies, and, most recently, surveillance registries that collect outcomes from pregnant patients who are treated with biologic agents. However, these registries are subject to bias because those who experience anomalies or adverse outcomes may be more likely to report such events.

Investigations into the role of TNF-alpha in embryogenesis in TNF-alpha knockout mice showed that TNF-alpha may play a role in the prevention of structural anomalies by either activating defense mechanisms that protect the embryo from harmful maternal stimuli or stresses or signaling for apoptosis if overwhelming detrimental signals occur (Toder et al., 2003).

In contrast, concern about the increased risk of congenital malformations, preterm birth, low birth weight, and spontaneous abortions have been raised about treatment with TNF-alpha inhibitors. For reference, according to the FDA, the risk of major birth defect is 2% to 4% and the rate of miscarriage is 15% to 20% in the U.S. general
population. Carter et al. (2006) originally published a case report and described an infant who was born with vertebral, anal, tracheal, esophageal, and radius or renal (VATER) association to a mother who was treated with etanercept. In 2009, the same author published another article that proposed a causal relationship between TNF-alpha inhibition and VATER association on the basis of a review of the FDA database of birth defects that were reported in mothers who were treated with TNF-alpha inhibitors (Carter et al., 2009). The methodology was controversial at the time, and further evaluation of larger registries failed to confirm this association (Koren and Inoue, 2009; Verstappen et al., 2011).

Still, conflicting data have been published about the general safety of biologic agents in pregnancy. A prospective, observational, multicenter cohort study that was conducted within the European Network of Teratology Information between 1993 and 2013 compared 495 pregnancies during which the patients were exposed to TNF-alpha inhibitors (adalimumab, certolizumab, etanercept, golimumab, and infliximab) with 1532 control subjects. The study concluded that those patients who were exposed to TNF-alpha inhibitors had a moderately increased risk of birth defects (of which no pattern could be ascertained), an increased risk of preterm birth and low birth weight, and no increased risk of spontaneous abortion (Weber-Schoendorfer et al., 2015). Unfortunately, the control subjects did not have disease, and, therefore, the authors could not attribute these findings to disease versus medication exposure. Of note when interpreting these findings, two population-based health registries of data from infants born to mothers with chronic inflammatory disease who were either exposed or not exposed to anti-TNF in utero found that birth defects were slightly more common in those infants who were born to mothers with chronic inflammatory disease regardless of whether they were treated with anti-TNF agents and that no specific pattern of defects could be found to suggest a common etiology (Bröms et al., 2016).

A 2014 review of 105 articles on the use of anti-TNF therapy in patients with IBD and pregnancy found that anti-TNF agents were safe during pregnancy, and the authors even recommended maintained use and initiation of therapy with anti-TNF agents for patients who were refractory to azathioprine, steroids, and 5-aminosalicylate (Khan et al., 2014). Clowse (2010) looked at the effect on pregnancy of infliximab, adalimumab, and etanercept both combined and individually compared with the general population and found no significant differences in the number of live-born infants, miscarriages, elective terminations, or congenital abnormalities.

### Treatment considerations for agents during pregnancy and breastfeeding

Historically, the FDA categorized medications into five categories: A, B, C, D, and X. Under the old FDA classification system, biologic agents were classified as a Pregnancy Category B: animal studies

<table>
<thead>
<tr>
<th>Biologic Agent</th>
<th>FDA Approval</th>
<th>Mechanism of Action</th>
<th>Structure</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certolizumab</td>
<td>PsA</td>
<td>TNF-alpha inhibition</td>
<td>PEGylated Fab' IgG fragment of humanized monoclonal antibody</td>
<td>Limited data: - Multiple studies (cohorts, case control, case reports/series) of more than 300 pregnancies show no increased risk of miscarriage or congenital malformation; however, no studies with control group available (Götestam Skorpen et al., 2016). - Low levels in cord blood, suggesting minimal active transplacental transport (Förger et al., 2016).</td>
</tr>
<tr>
<td>Cimzia</td>
<td>PsA</td>
<td>IL-17 inhibition</td>
<td>IgG1κ monoclonal antibody</td>
<td>Extremely limited data: - No human studies - Studies in mice and monkeys show no embryofetal toxicity</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>PsO</td>
<td>TNF-alpha inhibition</td>
<td>Fc Fragment of human IgG fusion protein</td>
<td>Limited data: - Multiple studies (cohorts, case controls, registry data, case reports/series) of more than 300 exposed pregnancies show no difference in miscarriage or congenital malformations compared with controls (Götestam Skorpen et al., 2016).</td>
</tr>
<tr>
<td>Cosentyx</td>
<td>PsA</td>
<td>TNF-alpha inhibition</td>
<td>IgG1 Fully human monoclonal antibody</td>
<td>Limited data: - Multiple studies (cohorts, case controls, registry data, case reports/series) of more than 500 exposed pregnancies show no difference in miscarriage or congenital malformations compared with controls (Götestam Skorpen et al., 2016).</td>
</tr>
<tr>
<td>Enbrel</td>
<td>PsO</td>
<td>TNF-alpha inhibition</td>
<td>IgG1 Mouse-human chimeric monoclonal antibody</td>
<td>Limited data: - Multiple studies (cohorts, case controls, registry data, case reports/series) of more than 5000 exposed pregnancies show no difference in miscarriage or congenital malformations compared with controls (Götestam Skorpen et al., 2016).</td>
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<tr>
<td>Adalimumab</td>
<td>PsO</td>
<td>TNF-alpha inhibition</td>
<td>Humanized IgG4 monoclonal antibody</td>
<td>Very limited data: - Few case reports/case series and limited registry data (Götestam Skorpen et al., 2016). - No increased risk of congenital defects or miscarriages (Götestam Skorpen et al., 2016). - One case report of spontaneous abortion is reported for a patient with other risk factors (Fotiadou et al., 2012).</td>
</tr>
<tr>
<td>Humira</td>
<td>PsA</td>
<td>TNF-alpha inhibition</td>
<td>Humanized IgG4 monoclonal antibody</td>
<td>Extremely limited data: - No human studies - One study in monkeys shows no harmful effect on the fetus when the medication was administered during the first 20 weeks of gestation. Medication administration from week 20 to birth showed an increase in neonatal deaths. No effects on the infants’ immune system development or maturation were noted at 6 months of age (Clarke et al., 2015).</td>
</tr>
<tr>
<td>Infliximab</td>
<td>PsO</td>
<td>TNF-alpha inhibition</td>
<td>Humanized IgG4 monoclonal antibody</td>
<td>Limited data: - Multiple studies (cohorts, case controls, registry data, case reports/series) of more than 1000 exposed pregnancies show no difference in miscarriage or congenital malformations compared with controls (Götestam Skorpen et al., 2016).</td>
</tr>
<tr>
<td>Remicade</td>
<td>PsA</td>
<td>TNF-alpha inhibition</td>
<td>Humanized IgG4 monoclonal antibody</td>
<td>Limited data: - Multiple studies (cohorts, case controls, registry data, case reports/series) of more than 500 exposed pregnancies show no difference in miscarriage or congenital malformations compared with controls (Götestam Skorpen et al., 2016).</td>
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<tr>
<td>Ustekinumab</td>
<td>PsA</td>
<td>TNF-alpha inhibition</td>
<td>Humanized IgG4 monoclonal antibody</td>
<td>Limited data: - Multiple studies (cohorts, case controls, registry data, case reports/series) of more than 1000 exposed pregnancies show no difference in miscarriage or congenital malformations compared with controls (Götestam Skorpen et al., 2016).</td>
</tr>
<tr>
<td>Stelara</td>
<td>PsO</td>
<td>IL-12/23 inhibition</td>
<td>Humanized IgG4 monoclonal antibody</td>
<td>Very limited data: - Few case reports/case series and limited registry data (Götestam Skorpen et al., 2016). - No increased risk of congenital defects or miscarriages (Götestam Skorpen et al., 2016). - One case report of spontaneous abortion is reported for a patient with other risk factors (Fotiadou et al., 2012).</td>
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<tr>
<td>Ixekizumab</td>
<td>PsO</td>
<td>IL-17A inhibition</td>
<td>Humanized IgG4 monoclonal antibody</td>
<td>Extremely limited data: - No human studies - One study in monkeys shows no harmful effect on the fetus when the medication was administered during the first 20 weeks of gestation. Medication administration from week 20 to birth showed an increase in neonatal deaths. No effects on the infants’ immune system development or maturation were noted at 6 months of age (Clarke et al., 2015).</td>
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</table>

Fab, antigen-binding fragment antibody; FDA, U.S. Food and Drug Administration; IgG, Immunoglobin G; IL, interleukin; PsA, psoriatic arthritis; PsO, psoriasis
breastfeeding may overall be safe for nursing mothers without significant risk while being treated with biologic agents, but recent data shows that levels of anti-TNF agents are very low (Clowse, 2010). Thus, many recommendations for the treatment of patients with psoriasis during pregnancy and breastfeeding. Current body of literature suggests that biologic agents can be used for the treatment with biologic agents during pregnancy, the increasing number of medications (FDA). It is worth noting that methotrexate, which is sometimes used in conjunction with biologic agents, is classified as Pregnancy Category X and has been linked to spontaneous abortion when administered in high doses.

In 2015, this five-letter system was changed due to concerns that it was oversimplified and did not accurately assess risk. The new FDA labeling requirement, the Pregnancy and Lactation Labeling Rule, went into effect on June 30, 2015 and provides more detailed information to healthcare providers in three categories: pregnancy, lactation, and females and males of reproductive potential. Under the pregnancy category, specific clinical summaries, data, and risk summaries are presented. Information about pregnancy registries is also required as part of the new labeling. This information is available under Sections 8.1 to 8.3, Special Populations, of the package insert of medications (FDA).

Although data on treatment with specific biologic agents during pregnancy has increased significantly in the last decade, the use of biologic agents in pregnant patients with psoriasis is less studied compared with treatment in patients with rheumatic disease or IBD. Thus, few data are available on more psoriasis-specific medications such as ustekinumab, secukinumab, and ixekizumab. A summary of available data on individual biologic agents is listed in Table 1.

Most package inserts for medications warn against breastfeeding while being treated with biologic agents, but recent data shows that breastfeeding may overall be safe for nursing mothers without significant risk to newborn babies. Low levels of TNF-alpha inhibitors can be detected in breast milk (Gisbert and Chaparro, 2013). However, because this milk is digested with gastric acid that is secreted by the baby, protein degradation likely occurs and makes newborn levels of anti-TNF agents very low (Clowse, 2010). Thus, many researchers have asserted that there is very little to no risk to the breastfed infant (Clowse, 2010). No specific data are available on the safety of breastfeeding and use of other biologic agents such as ixekizumab, ustekinumab, and secukinumab at this time.

Conclusions

Although no well-controlled trials have studied the effects of treatment with biologic agents during pregnancy, the increasing body of literature suggests that biologic agents can be used for the treatment of psoriasis during pregnancy and breastfeeding. Current recommendations for the treatment of patients with psoriasis during pregnancy are as follows. First, anti-TNF-alpha agents should be considered over IL-12/23 and IL-17 inhibitors due to the increased availability of long-term data. Second, anti-TNF-alpha agents can be used during the first half of pregnancy. Thus, a pregnancy with early, inadvertent exposure to anti-TNF alpha agents should not be considered at significant risk. Third, longer-term use of anti-TNF alpha agents during pregnancy can be considered depending on psoriasis disease severity. Fourth, if treatment with biologic agents is required throughout the pregnancy, use of certolizumab should be considered because it does not cross the placenta in significant amounts. Etanercept may also be a reasonable alternative because its placental transfer is less than adalimumab or infliximab. Fifth, babies born to mothers who are continually treated with biologic agents should not be administered live vaccinations for 6 months after birth due to the increased risk of infection. Inactive vaccinations can be administered in accordance with CDC-recommended guidelines. Sixth, breastfeeding by mothers currently treated with anti-TNF alpha biologic treatment regimens is generally considered safe due to the minimal amounts of medication that are present in breast milk and infant gastric digestion. Although actual data are primarily for anti-TNF agents, this safety profile is likely generalizable to the newer IL-12/23 and IL-17 inhibitors as well. Seventh, cotreatment with methotrexate and biologic agent should be avoided. Eighth, psoriasis as a disease is itself a risk factor for adverse pregnancy outcomes and perhaps control of disease prior to and during pregnancy may optimize maternal and fetal health.

Finally, adverse pregnancy outcomes should be reported to registries such as the Organization of Teratology Information Specialists or to manufacturer-sponsored pregnancy surveillance programs to increase our understanding of the effects of treatment with biologic agents during pregnancy and breastfeeding (Table 2).

References


Table 2
Pregnancy registries for select biologic agents

<table>
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<tr>
<th>Pregnancy Surveillance Program</th>
<th>Information Reported</th>
<th>Phone Number</th>
<th>Website</th>
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</thead>
<tbody>
<tr>
<td>Organization of Teratology Information Specialists (OTIS) via MotherToBaby</td>
<td>Collecting information on inflammatory and immune-mediated conditions and medications used to treat psoriasis and psoriatic arthritis, inflammatory bowel disease, rheumatoid arthritis, anklylosing spondylitis, and multiple sclerosis</td>
<td>1-800-222-4555</td>
<td><a href="http://mothertobaby.org/pregnancy-studies/">http://mothertobaby.org/pregnancy-studies/</a></td>
</tr>
<tr>
<td>Amgen Pregnancy and Lactation Surveillance Program for Enbrel (Etanercept)</td>
<td>Collecting information on pregnancy and lactation for patients taking Enbrel</td>
<td>1-800-77-AMGEN</td>
<td>(1-800-772-6436)</td>
</tr>
<tr>
<td>Janssen Pregnancy Registry for Stelara (ustekinumab)</td>
<td>Collecting information on pregnancy for patients taking Stelara</td>
<td>1-800-242-9511 to enroll</td>
<td></td>
</tr>
</tbody>
</table>
Clarke DO, Hilbish KG, Waters DG, Newcomb DL, Chellman GJ. Assessment of ixekizumab, an interleukin-17A monoclonal antibody, for potential effects on reproduction and development, including immune system function, in cynomolgus monkeys. Reprod Toxicol 2015;38:160–73.


