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Letter to the Editor

# Considerations on biologic agents in psoriasis with the new pregnancy lactation labeling rule☆

Psoriasis is a complex chronic disease that can be challenging to manage, especially during pregnancy. The course of psoriasis can fluctuate throughout pregnancy as hormone levels change. In the only prospective study of pregnant patients with psoriasis, it was found that 55% of the patients reported improvement during pregnancy, 21% reported no change, and 23% reported worsening of psoriasis. However, postpartum, only 9% of patients reported improvement, 26% reported no change, and 65% reported worsening psoriasis. High levels of estrogen correlated with improvement in psoriasis, whereas progesterone levels did not correlate with psoriatic change (Murase et al., 2005).

It is now well known that Th1 and Th17 immunity plays a role in the current model of psoriasis pathogenesis. It has also been shown that pregnancy can be associated with diminished Th1 and Th17 mediated immunity, mainly due to the effects of increased estradiol. It is postulated that this increase promotes fetal survival by decreasing responses involved in rejection of the fetus (Sacks et al., 2001; Santner-Nanan et al., 2009). With all of these dynamics at play, it can be difficult for dermatologists to manage psoriasis in pregnant patients while protecting the fetus and mother.

When identifying medications and treatments to use in psoriasis patients during pregnancy, the old lettering categories of A, B, C, D, and X have served as surrogate markers of risk stratification. A review of treatment options for pregnant psoriasis patients found that most treatment options fall under category C, indicating that controlled studies in humans either have not been performed or are not available (Bae et al, 2012). Additionally, the 2012 National Psoriasis Foundation (NPF) consensus guidelines for treatment of all psoriasis patients propose first-line treatment with moisturizers and topical corticosteroids (preferably low to mid potency); second-line treatment with narrowband or broadband ultraviolet B; and third-line treatment with tumor necrosis factor inhibitors (adalimumab, etanercept, infliximab), cyclosporine, or systemic steroids (in second and third trimesters only). The NPF guidelines also state that systemic and biologic agents should be avoided in pregnancy and lactation unless there is a clear medical need (Chi et al., 2010). However, two major changes have occurred since the release of these guidelines that dermatologists should take into consideration. The introduction of a new pregnancy safety labeling system and the surge of newer biologic agents for the treatment of psoriasis into the marketplace will affect treatment options for pregnant patients.

Dermatologists should be knowledgeable about the recent Food and Drug Administration (FDA) changes in the way pregnancy safety is labeled on drugs. Effective June 30, 2015, the FDA released their Pregnancy and Lactation Labeling Rule (PLLR) which will be phased in over the next 3 years for existing drugs and required for all new drugs. The PLLR will introduce changes that aim to improve the communication and decision-making process between physicians and patients. The PLLR has several main changes, including the removal of pregnancy lettering categories; compression of population categories (e.g., pregnancy, labor and delivery, nursing mothers); and the implementation of a new risk narrative section. The PLLR will abolish lettering categories entirely and replace them with an individualized narrative summary of each drug which will include "risks of using a drug during pregnancy and lactation, a discussion of the data supporting that summary, and relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation" (FDA, 2014). It will also create new populations labels, with the former labels of "Pregnancy" and "Labor and Delivery" being combined and placed into a single category of "Pregnancy." The former population label of "Nursing Mothers" will now be placed into the label of "Lactation." Additionally, there will be an entirely new label of "Females and Males of Reproductive Potential," which will discuss contraception recommendations, pregnancy testing, and information surrounding infertility associated with medication use.

The new changes introduced by the PLLR will aim to improve the former pregnancy lettering system, which has been criticized for being overly simplified, ambiguous, and incomplete (Addis et al., 2000; Boothby and Doering, 2000; Doering et al., 2002). This new narrative system will not only remove some of the prior ambiguity from the lettering system, but it will also present more information for physicians and patients to create a more individualized clinical decision. Additionally, this will help to reduce the "innocent until proven guilty" status that is placed on drugs, where untested drugs without any known harmful side effects are perceived to be safer (category B) than tested drugs with known side effects (category C). This narrative will provide more explicit detail on the sources of information and data pertaining to drugs. For example, the pharmaceutical drug pregnancy data information is obtained from animal studies in 92.9% of drugs, and only 5.2% obtained from human pregnancy data (Chambers, 2014; FDA, 1999; Mazer-Amirshahi et al, 2014). This kind of information will be made explicit in the new PLLR.

Since the last NPF guidelines on treatment of psoriasis in pregnancy were released in 2012, new biologic agents have come to market, with many more in the research pipeline. Currently, two new agents are on the market: an anti–interleukin (IL)-17 agent, secukinumab, approved for moderate to severe plaque psoriasis in January 2015; and the small molecular inhibitor, apremilast, a phosphodiesterase

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4 inhibitor approved for moderate to severe plaque psoriasis in September 2014. Many other biologic agents and small molecule inhibitors are in the pipeline: anti–IL-17 agents such as ixekizumab, and brodalumab, and anti–IL-23 agents such as tildrakizumab and guselkumab (Mansouri and Goldenberg, 2015). Although phase 2 and 3 data from these drugs show very promising results for the treatment of psoriasis, additional considerations must be taken when treating pregnant psoriasis patients (Griffiths et al., 2015; Langley et al., 2015; Lebwohl et al., 2015). From these preliminary results, it appears that these drugs have similar safety profiles, with the most frequently reported adverse events being nasopharyngitis, upper respiratory infections, headache, and injection site reaction (Mansouri and Goldenberg, 2015). These adverse events are similar to those seen in older biologic agents such as adalimumab, etanercept, and infliximab (Mendes et al., 2014).

Few data are available evaluating the safety in pregnancy for adalimumab, etanercept, and infliximab, with an even further paucity of data regarding the newer biologic agents discussed. Several case series, case reports, and retrospective studies have concluded that adalimumab, etanercept, and infliximab have all been consistent with the old FDA categorization of pregnancy class B (Berthelot et al., 2009; Carter et al., 2006; Kane et al., 2009; Katz et al., 2004; Mahadevan et al., 2005; Mishkin et al., 2006; Murashima et al., 2009; Rump and Schönborn, 2010). This is all consistent with the 2012 NPF recommendations that these drugs should be regarded as third-line treatments for pregnant psoriasis patients (Bae et al., 2012). For these reasons and the changing PLLR classification system, we propose to update the recommendations to include the newest generation of biologic agents for psoriasis. Given that the advent of the newest generation of biologics is not mentioned in the 2012 guidelines, we endorse the extension of the same recommendations to all pregnant psoriasis patients for the anti–IL-17 agents (secukinumab, brodalumab, ixekizumab) and anti–IL-23 agents (BI 655066, guselkumab, tildrakizumab). These drugs, which are either currently on the market or in the pipeline, have demonstrated theoretical immunosuppressive risk and safety profiles similar to the previous generation of biologics and should be considered as such in pregnant psoriasis patients (Manalo et al., 2015; Mansouri and Goldenberg, 2015).

Although the new PLLR labeling system will provide additional narrative and data to the selection process of drugs in pregnancy, it will take time before adequate data are available to construct an acceptable narrative. Until all of the data are in, it may be the best course of action to continue with first- and second-line treatment modalities for pregnant psoriasis patients and consider the new biologic agents as third-line treatment options. All physicians are encouraged to review the new labeling rules (Federal Register, 2014) in order to promote a smooth transition. For a more condensed version of the PLLR, please see U.S. Department of Health and Human Services (2014). Drug labels may be found at Dailymed (http://dailymed.nlm.nih.gov/dailymed/index.cfm).

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