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Management of moderate to severe plaque psoriasis in pregnancy and lactation in the era of biologics

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Abstract

Psoriasis is not uncommon in the reproductive years and therefore in pregnant patients. There are limited data about the impact of psoriasis on the course and prognosis of pregnancy and about the impact of pregnancy on the course of psoriasis. Usually the disease improves during pregnancy and patients experience worsening between 4 and 6 weeks after delivery. A safe option for patients with limited disease is topical therapy, including moisturizers and topical steroids as well as UVB phototherapy. In the case of active psoriasis or even psoriasis worsening during pregnancy, there might be a need for continuation or even introduction of systemic therapy. Methotrexate and acitretin are known teratogens and mutagens, and they must be avoided. Ciclosporin may be regarded as a possible rescue therapy for pregnant psoriasis patients in the case of severe disease. Post-marketing experience regarding the safety of biologics is accumulating, with largely reassuring results. All four biologics approved for the treatment of moderate to severe psoriasis–etanercept, infliximab, adalimumab, and ustekinumab–are not currently recommended in pregnant psoriasis patients. The existing evidence implies that the risk of biologics in pregnancy is relatively low and that the risk of fetal drug exposure may be outweighed by the benefits for the mother.

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Introduction

Psoriasis vulgaris is a chronic immune-mediated inflammatory skin disease. It accounts for more than 80% of all cases of psoriasis (1). Moderate to severe psoriasis is considered a systemic disease with several psoriasis comorbidities such as metabolic syndrome, psoriatic arthritis, depression, and anxiety (2).

The severity of psoriasis must be assessed for proper management of the disease. Mild psoriasis is defined as body surface area (BSA) ≤ 10 and psoriasis area and severity index (PASI) ≤ 10 and dermatology life quality index (DLQI) ≤ 10. Moderate to severe psoriasis is defined as BSA > 10 or PASI > 10 and DLQI > 10. Some special clinical situations such as involvement of visible areas, face, scalp, genitals, palms, and soles may change mild psoriasis to moderate or severe despite the lesser extent of affected skin. Mild disease is most commonly successfully managed topically, and in refractory psoriasis with the addition of phototherapy. Moderate to severe psoriasis cannot be successfully controlled with topical therapy, and therefore phototherapy and systemic therapy are the recommended methods of treatment (3, 4).

The prevalence of psoriasis ranges from 2 to 3% in the Caucasian population. Women and men are affected equally, and the disease usually starts between the second and fourth decades of life. The average age of diagnosis in women is 28. These are the reproductive years and therefore psoriasis is not uncommon in pregnant patients (1). It is estimated that in the United States there is a range of approximately 65,000 to 107,000 births to women with psoriasis annually, of whom 9,000 to 15,000 have moderate to severe disease (5).

Moderate to severe psoriasis may lead to complications in the course of gestation, preterm delivery, and low birth weight (6). A large study that included 1,463 mothers with psoriasis and 11,704 randomly selected mothers without the disease showed that pregnant women with severe psoriasis had a higher risk of giving birth to a newborn with low birth weight. They observed an increased risk of complications such as premature labor, cesarean delivery, and preeclampsia among pregnant psoriasis patients treated with systemic therapy. Conversely, mothers with mild psoriasis had no significantly higher odds for complications during the course of pregnancy (7). The influence of pregnancy on the clinical course of psoriasis is unpredictable; however, usually the disease improves during pregnancy and patients experience worsening between 4 and 6 weeks after delivery. In a study of pregnant psoriasis patients, 55% reported improvement, 21% experienced no change, and 23% reported worsening of disease. Postpartum, only 9% of patients experienced improvement, 65% worsened, and 26% showed no appreciable changes in disease activity (8). In another retrospective study of 91 pregnant women with psoriasis, 56% of patients experienced improvement, 18% remained unchanged, and 26% worsened (9). Improvement could probably be attributed to the immunoendocrine interactions observed in pregnancy with a higher ratio of estrogen to progesterone (10).

Management of psoriasis in pregnancy and lactation

Dermatologists are faced with questions about the safety of different therapeutic modalities during gestation and lactation. Teratogenic and other possible adverse risks for the child must be balanced with the risk from uncontrolled skin inflammation affecting the course of pregnancy and postpartum period. Adjustment of therapy in a patient planning to become pregnant or during early pregnancy is needed.

Currently there are limited data on the safe administration of drugs during pregnancy. Pregnant women are excluded from prospective clinical trials due to ethical reasons. Knowledge only slowly accumulates from inadvertent as well as intentional drug exposure during pregnancies in the form of case reports and various registry collectives. Valuable data on the safety of systemic drugs for treating psoriasis can be drawn from the larger population of inflammatory arthritis and inflammatory bowel disease patients treated with the same agents while pregnant and breastfeeding. Another source of information on the safe use of

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drugs in pregnancy is the US Food and Drug Administration (FDA) pregnancy categories system (Table 1) (11, 12).

Patient counseling before conception is invaluable. A woman with psoriasis of reproductive age should be asked about her childbearing plans in order to choose appropriate medications and provide education (13). About half of patients with psoriasis experience improvement or remission during pregnancy (8, 9). An option for these women may be discontinuation of medications or topical therapy including moisturizers and low- to moderate-potency topical steroids or UVB phototherapy. These represent the first-line therapy for pregnant or breastfeeding psoriasis patients, provided the disease is limited (11, 13). If moderate to severe psoriasis remains active or even worsens during pregnancy, there might be a need for continuation of systemic treatment. Some of these medications are known teratogens and mutagens, and they must be avoided. Others may be used relatively confidently.

Methotrexate

Methotrexate has been widely used in the systemic treatment of moderate to severe psoriasis since 1958 due to its efficacy, extensive clinical experience, and low cost (14). It inhibits the synthesis of DNA by competitive binding to dihydrofolate reductase and has been known as an abortifacient, as well as a mutagen and teratogen agent in animals and humans. It is classified as FDA category X and is absolutely contraindicated during pregnancy. The sensitive period for the occurrence of malformations is between 6 and 8 weeks after conception and the dose required to produce defects is greater than 10 mg per week (16). The abnormalities can occur even in doses lower than 10 mg weekly (16). Methotrexate increases the risk of abortion and birth defects, such as central nervous system, craniofacial, limb, gastrointestinal, and cardiopulmonary malformations, as well as growth delay (15, 17, 18). Because 6 to 8 weeks after conception is the critical period for abnormalities, a "washout" period of at least 3 months is advisable before conceiving, and supplementation with folic acid during this period and throughout pregnancy is recommended (15). Methotrexate has been linked to disturbances in spermatogenesis, such as chromosomal abnormalities and alterations in the sperm mobility. However, a prospective study of 42 fetuses whose fathers were exposed to weekly doses between 7.5 and 30 mg 3 months before or until conception reported no birth abnormalities (19). Methotrexate is transferred into breast milk in significantly lower concentrations compared to maternal serum. It could be present in child tissues for months and therefore it should not be used during lactation (11, 20, 21).

Ciclosporin

Ciclosporin has been classified as a traditional systemic agent for psoriasis treatment and has been approved for this indication since 1993. It is usually given as a short-term therapy for 2 to 4 months (4). It is a selective immunomodulator by acting as a calcineurin inhibitor (22). The drug passively crosses the placental blood barrier to achieve 10 to 50% of the maternal plasma concentration (23). It is not teratogenic in animals or humans. It is classified as FDA category C. There are limited data on the effect of ciclosporin in pregnant psoriasis patients. The majority of information on its use during pregnancy derives from registries of transplant recipients, who usually receive higher doses than psoriasis patients. The drug has no mutagenic properties; namely, no increase of congenital malformations nor any special malformation pattern has been noted. However, there was an increased risk of premature delivery and low birth weight (24–26). Ciclosporin is not absolutely contraindicated in pregnancy and has been used successfully in pregnant women. It may be regarded as a possible rescue therapy for pregnant psoriasis patients in the case of severe disease after thorough risk and benefit analysis together with the patient (11). Cyclosporine is excreted in breast milk at variable levels. Although there are reports of safe infant exposure during lactation with normal development and growth, the current recommendation is that breastfeeding should be avoided while taking ciclosporin due to concerns of immunosuppression in the infant (4, 27).

Acitretin

Acitretin belongs to the group of retinoids. The exact mechanism of action has not been completely clarified, although it affects cellular differentiation and proliferation. Due to lack of efficacy given as a monotherapy, it is no longer suggested among the first-choice therapies for moderate to severe psoriasis patients (4). Acitretin is a well-known teratogen probably acting by affecting cellular differentiation and proliferation. It is classified as FDA category X and is absolutely contraindicated during pregnancy. Acitretin administered in the first trimester of pregnancy increases the risk of spontaneous abortion and congenital defects, such as central nervous system, craniofacial, limb, thymic, and cardiovascular malformations (28). Therefore pregnancy should be avoided during and up to 2 years after the end of therapy, which makes acitretin an impractical and unsuitable therapy for women in their reproductive years. Despite the short elimination half-life of acitretin of only 2 days, it can be converted in small amounts to etretinate with a much longer

Table 1 | **U.S. FDA categories for drug safety during pregnancy.**

FDA pregnancy category	Definition
A	Controlled studies in animals and women have shown no risk in the first trimester, possible fetal harm is remote
B	Animal reproduction studies have failed to demonstrate risk to the fetus but there are no well-controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect that was not confirmed in well-controlled studies in pregnant women in the first trimester of pregnancy
C	Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, or there are no animal reproduction studies and no adequate and well-controlled studies in humans
D	Evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks if life-threatening or serious disease
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, drug is contraindicated

half-life of 100 days, especially by concomitant intake of ethanol. Therefore, women of childbearing age should be discouraged from taking acitretin, and in the case of using this treatment the decision to avoid pregnancy is mandatory. The drug should be introduced on the second or third day of the menstrual cycle, after at least 1 month of satisfactory double contraception. Monthly pregnancy tests are recommended (4).

Literature reports only minimal excretion of acitretin into breast milk; however, breastfeeding should be avoided due to the potential for cumulative neonatal toxicity (21, 29).

Biologics

Currently four biologic agents are approved for moderate to severe psoriasis treatment, which is inadequately controlled with conventional systemic agents or if these agents are contraindicated. Etanercept, infliximab, and adalimumab belong to the TNF inhibitors, which prevent the activation of TNF-α receptor by binding to circulating TNF-α. Ustekinumab is an IL-12/23 inhibitor that blocks the activity of IL12 and IL23 by binding to their p40 subunit. According to current manufacturers' recommendations, all biologic agents should be discontinued for variable periods of time prior to conception depending on elimination half-life and the duration of the biologic effect of these drugs. Reliable contraception should be introduced. Etanercept should be discontinued at least 3 weeks prior to conception. The intervals for infliximab, adalimumab and ustekinumab are at least 6 months, at least 5 months, and up to 15 weeks, respectively (30). The reason for these guidelines is a lack of controlled studies of biologics in pregnant women. However, postmarketing experience regarding the safety of these drugs is accumulating and being published, with largely reassuring results. All four approved biologics for psoriasis treatment are classified as Pregnancy FDA category B, which means there is no risk from animal studies; however, there are no adequate and controlled studies in women receiving biologic agents during pregnancy (11, 13). Experience with exposure to biologics in pregnancy is slowly accumulating, especially in the setting of inflammatory bowel disease and inflammatory arthritis patients. In the case of unplanned conception, most women stop the biological therapy at the time of pregnancy confirmation (31).

Despite some isolated reports of congenital malformations in children exposed to biologics during pregnancy, data from various inflammatory bowel disease and rheumatologic registries show that major congenital malformations after exposure to biologics prior to conception or during the first 3 months of pregnancy occur at rates that are lower than the estimated population rate, which is approximately 3% (32, 33). No specific or consistent pattern of malformations connected to exposure to biologics has been reported so far (34–36). A large collection of 131 pregnancies exposed to infliximab from the Centocor safety database reported no increased risk of adverse outcomes such as miscarriages, therapeutic terminations of pregnancy, and congenital malformations when compared with the general population (37). The OTIS (Organization for Teratology Information Specialists) registry reported 100 pregnancies exposed to etanercept, which had similar live birth rates and similar rates of major congenital malformations compared to a control group of pregnant patients with inflammatory arthritis not exposed to etanercept (38). The same registry reported 66 pregnancies exposed to adalimumab for rheumatoid arthritis during the first trimester, comparing them to non-adalimumab treated patients and healthy controls. There was no increased risk or evidence of a specific pattern of major or minor birth defects connected with adalimumab exposure (39). Ustekinumab is a relatively new biologic drug and experience during pregnancy is extremely limited. One reported case of its use during pregnancy in a psoriasis patient reported an uncomplicated pregnancy and a healthy infant delivered at term (40). Accumulated data may be reassuring that termination of pregnancy is not necessary for women that inadvertently become pregnant while taking biologics. An exposure to biologics during the first trimester does not seem to hold an increased risk of congenital defects or other unfavorable outcomes of pregnancy.

The structure of infliximab, adalimumab, and ustekinumab is an IgG1 monoclonal antibody, whereas etanercept is a fusion protein. It is well known that maternal IgG antibodies are large hydrophilic proteins of more than 100 kDa and cannot cross the placenta by simple diffusion, but are actively transported via Fc receptors on the syncytiotrophoblast. These receptors have not been observed before week 14 of gestation; however, the active transport of IgG immunoglobulins begins during the second trimester and rapidly increases over the third trimester, leading to higher fetal levels of IgG in comparison to those in maternal circulation. The half-life of immunoglobulins in an infant is considerably longer than in adults (41–43). Infliximab, adalimumab, and ustekinumab are actively transported through the placenta in the same way as natural maternal antibodies reaching high blood levels in the newborn after being exposed in the late second and third trimester. Both infliximab and adalimumab have been found in newborns in much higher concentrations than in their mothers' peripheral blood, and they remain detectable from 2 to 7 months after birth. The median concentration of infliximab measured in cord blood at delivery was 160% of maternal, whereas the median concentration of adalimumab in cord blood was 153% of that detected in maternal serum (44–46). There is no published human study on ustekinumab so far; however, in an animal study on cynomolgus macaques ustekinumab was detected in fetal serum as well as in the serum of infants as long as 120 days postpartum (47). Etanercept, on the other hand, shows considerably less transplacental transport than the IgG immunoglobulins. The concentration of etanercept in cord blood after treatment in the second and third trimester was 4 to 7% of that in maternal blood (48, 49).

There is a concern that the use of biologics that actively cross the placenta during pregnancy could result in immunosuppression in a newborn and increase the risk of infection. One case of a fatal disseminated bacillus Calmette-Guérin (BCG) infection after regular vaccination in an infant delivered to a mother with Crohn's disease that was treated throughout pregnancy with infliximab was reported (50). Therefore, infliximab, adalimumab and ustekinumab, which are IgG antibodies, should be discontinued as soon as pregnancy is recognized or in the case of difficult-to-control disease at least before gestational week 30 or preferably between weeks 20 and 22. This would probably limit significant intrauterine and postnatal drug exposure of an infant and, likewise, the risk of infection (36, 51).

The administration of live vaccines in a newborn that was exposed to biologic medication during the late second and third trimester should be postponed until 6 to 7 months of age or until the biological agent is no longer detectable in the infant circulation (13, 31, 36). Routine vaccinations with non-live vaccines appear to be safe and responses appear to be appropriate (44, 46).

Breastfeeding during therapy with biologics is not generally recommended, although the levels of the drugs detectable in

breast milk are significantly lower than those in maternal circulation. Two to 3 days after the infusion of infliximab, the milk concentration was 1/200 of that in maternal serum (52). Six days after injection of adalimumab, the level of drug detected in milk was 1/100 of that in maternal serum (53). Etanercept was detected in milk in extremely small concentrations; namely, 1/800 of that in maternal serum (49). Absorption of a biologic drug from milk is probably minimal because of protein structure degradation in the infant's digestive system. Therefore biologic medications could be compatible during breastfeeding (13, 31, 54).

There are limited data on men exposed to biologic drugs at the time of conception. So far there are no specific reports on adverse pregnancy outcomes (37, 55).

Conclusion

Pregnant and lactating women with psoriasis should be managed with caution. Topical therapy including emollients and topical steroids as well as UVB phototherapy is regarded as a safe option for these patients. In the case of uncontrollable psoriasis and a need for more potent systemic treatment, methotrexate and acitretin must be strictly avoided. However, ciclosporin may be considered as an option for controlling the disease. Newer biologic agents are currently not recommended due to a lack of controlled studies in pregnant women. Information regarding their use during pregnancy and lactation is slowly accumulating, mostly from pregnant patients with inflammatory arthritis and inflammatory bowel disease. Biologics may be considered as a possible therapy for pregnant psoriasis patients. Data collected so far show that biologics currently marketed for psoriasis treatment are not connected with higher incidence of unfavorable pregnancy outcomes and congenital malformations. There are concerns about immunosuppression in infants exposed to biologics in the late second and third trimesters of pregnancy, especially to monoclonal IgG antibodies such as infliximab, adalimumab, and ustekinumab. These drugs actively cross the placenta similarly to natural antibodies, leading to higher infant drug levels at delivery compared to the levels in maternal circulation, and they should be discontinued at least in the second trimester to limit significant intrauterine and postnatal drug exposure of an infant and the risk of infection. The administration of live vaccines in a newborn exposed to biologic medication during the late second and third trimesters should be postponed at least until 6 to 7 months of age. Breastfeeding during therapy with biologics is currently not recommended; however, it could be considered reasonable in the future because only negligible amounts of drug pass into the milk. The decision to use biological therapy during pregnancy should take into account benefits and risks and should be made on a case-by-case basis after careful discussion with the patient.

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