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REVIEW

Management of psoriasis in pregnancy – a review of the evidence to date

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Abstract

The onset of psoriasis collides with women's reproductive timeframe, and pregnancy brings challenges to its treatment. Indeed, the health of both mother and foetus must be considered. When choosing to treat pregnant women affected by psoriasis with pharmacological therapy, it is important to be aware of all possible options and their repercussions. Although there are several pharmacological therapies available, pregnancy brings ethical concerns and any pharmacological approach must be well thought out. The data available in humans are limited, and further investigation on this matter is needed. Within biological therapies, certolizumab pegol has recently been identified as a promising approach during pregnancy because it has been shown to have no late active placental transfer and no clear signs of foetal harm. This article aims to review the impact of psoriasis during pregnancy, how the disease can be managed pharmacologically during this period according to the available armamentarium, and the possible effects of the therapeutic options for the mother and the foetus.

Keywords: pregnancy, pregnancy complications, psoriasis, therapy.

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Introduction

Psoriasis is a chronic, inflammatory, systemic disease with typical skin lesions.[1,2] This disease represents an important public health challenge, affecting around 2.5% of the general population.[1,2] Psoriasis is associated with several comorbidities, including psoriatic arthritis, metabolic syndrome, cardiovascular diseases, inflammatory bowel diseases, and depression.[1,3] The significant physical and psychological burden of the disease has a negative impact on the patient's quality of life and potentially on long-term survival.[1,3]

Psoriasis is an immune-mediated disease affected by environmental and genetic factors.[1,4] Its pathogenesis involves both the innate and the adaptive immune compartment, with overproduction of several cytokines, such as Interleukin(IL)-1, IL-2, IL-6, IL-8, IL-12, IL-13, IL-17, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-36, interferon (IFN)-γ, IFN-α and tumour necrosis factor (TNF)-α.[1,4] The IL-23/IL-17 immune axis has been identified as a major immune pathway in the immunopathogenesis of psoriasis.[1,4]

Women with psoriasis may become pregnant, which brings about challenging concerns in the treatment of the disease. The health of the mother and the foetus must be considered when managing psoriasis during pregnancy.[5,6]

This article aims to review the impact of psoriasis during pregnancy, the treatment options available for psoriasis in pregnant women, and its expected effects on both mother and foetus. A search of the PubMed database (up to December 2019) for articles with the specific keywords 'psoriasis; pregnancy; therapy' present in the title, abstract, or body was performed. The reference lists of those articles were examined to retrieve other studies that were considered relevant and contributed to the scientific purpose of this review but had not been retrieved by the database search.

Psoriasis and pregnancy

The first symptoms of psoriasis usually occur between the second and fourth decades of life.[1] Thus, the onset of the disease collides with women's reproductive years, and it is not uncommon to see psoriasis in pregnant women.[1,7–9]

Pregnancy entails a unique challenge for the maternal organism, involving remarkable endocrine and immunological changes.[7–10] The course of psoriasis during pregnancy is very unpredictable.[7–9]

Most women experience an improvement in their symptoms, others maintain a stable state, but there is a subset of women in which an exacerbation of the disease is observed.[7–10]

The impact of maternal psoriasis on the development of the foetus is a point of concern. Studies described several adverse foetal outcomes, like spontaneous abortion, prematurity, macrosomia, weight-related disturbances (from large-for-gestational age to low birth weight) and a higher need for caesarean delivery. However, these associations were inconsistent and require further investigation.[5,6,10]

A severe disease may have a negative impact on both mother and foetus. This highlights the importance of measuring the risks of treating or not treating psoriasis during pregnancy.

Managing psoriasis during pregnancy

General considerations

The first trimester corresponds to the period of pregnancy with the highest chance of drug-induced teratogenicity. However, even when patients are being treated with drugs with potential teratogenic effects, couples' adherence to pregnancy prevention is considerably poor.[6]

Counselling before pregnancy is an issue of major importance. It provides not only education but also the timely decision on the most adequate therapeutic regimen having in view the possibility of pregnancy.[6,9,11] Psoriasis should either be controlled or in remission before conception to minimize possible flares during the pregnancy.[6,11]

During the pregnancy, the decision of treating psoriasis and how to manage the treatment options demands careful thought because the health of both the mother and the foetus must be brought into consideration. The goal is to attain the best possible disease control. Consideration must encompass not only the extent and severity of the disease but also the principle of not affecting the development of the foetus. Even with this in mind and due to obvious ethical constraints of performing clinical trials on pregnant women, there are limited data on this matter.[12] The majority of information comes from inadvertent foetal exposure to treatment for psoriasis on women who were unaware of their pregnancy.[9,13]

In pregnant women with mild psoriasis or in those experiencing an improvement of the disease during pregnancy, discontinuation of medication can be an option. However, this might not be the best choice for those with severe psoriasis. It is mandatory to acknowledge the risks for pregnancy for each kind of treatment option.[9,13]

Concerns about medication use during pregnancy have been highly enhanced since the 1960s when thalidomide showed deleterious effects on the foetus.[14] Further investigation on drugs with potential teratogenic effects has been undertaken and governmental agencies have reinforced the regulation about these drugs. Further data on animals and humans have been presented and to summarize the information obtained, classification systems have been established to help physicians.[15]

A source of information on the safety of drugs during pregnancy is given by the United States Food and Drug Administration (FDA). A system emerged in 1979 and was based on the classification of drugs into one of five letter system: A, B, C, D, and X (Table 1). The categorization is based on animal and human studies and uses data that outweigh the risk of adverse effects against the potential benefits of the drug.[16] This categorization into letters has been helpful in clinical practice as replacing markers of risk stratification.[16]

However, this classification system has often proved to be confusing, overly simplistic, and a limited way to reflect the available information, which may lead to false assumptions about the drugs based on their category alone.[15,17] According to this data, in 2015, the FDA introduced a new Pregnancy and Lactation Labeling Rule (PLLR), which replaces the letter rating system by narrative-based labelling requirements, with the intention

Table 1. US FDA pregnancy risk category definitions.

A	Controlled clinical trials in females failed to show a risk to the foetus in the first trimester, and the possibility of harm to the foetus appears remote
B	Either animal studies did not show a risk to the foetus and no controlled human studies are available, or animal studies showed an adverse effect on the foetus but well-controlled clinical trials in pregnant females have failed to demonstrate a risk to the foetus
C	Animal studies have shown teratogenic or embryocidal effects, but there are no controlled clinical trials in females, or no studies are available in either animals or humans
D	Positive evidence of foetal risk exists in humans, but benefits in certain situations may justify the use of the drug despite its risks (e.g. in life-threatening situations or in cases where safer drugs cannot be used or are ineffective for treatment of serious diseases)
X	Studies in animals or humans have shown foetal abnormalities, or there is evidence in humans of foetal risk, or both, and the risk outweighs any possible benefit

FDA, Food and Drug Administration.

This table was adapted from: https://www.drugs.com/pregnancy-categories.html

of promoting a discussion with patients about the risks and benefits of the drugs and thus favouring an informed decision.[18] The application of this new system has been phased into existing medications. Drugs that have been approved after 30 June 2015 must necessarily fulfil the new PLLR.[14] For these drugs, a safety category may not be assigned as they were replaced with an individualized narrative summary of each drug.[14]

In 2008, the European Medicines Agency (EMA) also provided a guideline on risk assessment of drugs during pregnancy and lactation.[19] According to this guideline, a drug may be classified as not responsible for a 10-fold or greater increase in the overall incidence of malformations if there is no increase in the number of malformation events in the follow-up of 300 first-trimester pregnant women who were exposed to the drug. If the pool of pregnant women observed is increased to 1000, then it is possible to reach the conclusion that the drug is not responsible for a two-fold or greater increase in the overall incidence of malformations.[19] Conversely, based on the level of association of the drug with adverse effects in pregnant women, a conclusion of a suggested/suspected or a demonstrated malformative effect of the medicinal product can be reached and this information should be labelled, according to this guideline.[19] The non-clinical assessment and consequent labelling should be based on all toxicological (e.g. reproductive toxicity studies) and pharmacological data available.[19]

With the establishment of PLLR being so recent, there are therapeutics currently on the market that are still attached to the previous categorization system, along with other drugs that already follow the new system given by PLLR.

Taking these aspects in consideration, in this review, reference to FDA categorization system will be made, if applicable, as well as other important data existing on the use of each treatment, despite limited human data for many of the reviewed drugs. Therapeutic options will then be approached according to their profile in terms of their adverse effects on pregnancy. Table 2 summarizes relevant information regarding the different therapeutic options.

Topical therapies

The first-line treatment during pregnancy is topically administered drugs.[5,11,20] When used judiciously, there is no substantial systemic absorption. Consequently, systemic levels high enough to cause adverse effects on the foetus will not be obtained. However, overdose increases the risk of teratogenicity.[13]

For limited disease, emollients and moisturizers should be the priority as they are well tolerated without significant adverse outcomes.[20]

Topical corticosteroids, when used appropriately (with the least potency required, and judicious monitoring of duration and amount of application), are assumed as safe for childbearing women.[21,22] The FDA classifies topical corticosteroids as category C. Although there is no causal association between topical corticosteroids of all potencies and the risk of development of most foetal abnormalities, it is stated that preference should be given to mild-to-moderate potency topical corticosteroids.[12,21,22] Potent or superpotent topical corticosteroids should be used as second-line therapy as the current evidence indicates they are probably associated with a higher likelihood of low birth weight, particularly for large amounts of cumulative exposure. In these cases, meticulous obstetric care is mandatory.[21,22]

Topical calcineurin inhibitors such as tacrolimus are occasionally applied to small areas of sensitive skin on intertriginous areas and face.[12] It is known that, in both animals and humans, tacrolimus present in systemic circulation can cross into the foetal circulation and has been related to low birth weight, prematurity, transient neonatal hyperkalemia, and renal dysfunction.[23–26] Nevertheless, the topical route of administration of calcineurin inhibitors is poorly associated with systemic absorption, and so this application route is expected to be safe.[6] Actual recommendations are that additional data on the topical use of this drug in pregnant women is required. The FDA classifies topical calcineurin inhibitors as category C.[6,12]

Within topical agents, the use of anthralin (dithranol) is not currently approved during pregnancy, as there is not enough data in humans or animals.[6,20] The FDA has assigned this drug as category C, and it should be stopped 4 weeks before conception.[6].

There is also limited data regarding the use of salicylic acid during pregnancy.[6,20] A moderate amount (up to 25%) of the applied drug can be absorbed by the systemic circulation and can cause deleterious effects to foetus.[6,27] Therefore, if it cannot be avoided, its use should be limited to low-to-moderate concentrations (<3%), and pregnant women should avoid large amounts (>20 g per day) as well as use under occlusion to prevent from adverse effects.[6] The FDA assigned this drug as pregnancy category C.[6,14,20]

Systemic absorption may occur with topical vitamin D analogues, such as calcipotriol.[12,13,28] There are no studies in humans reporting teratogen effects during pregnancy.[12,20,28] However, there are studies in animals that correlate the administration of calcipotriol with a higher incidence of skeletal abnormalities, such as incomplete ossification of forelimb phalanges and pubic bones.[6] Therefore, although the recommended topical dosage is considered safe, caution is required, as no human data are currently available.[12,20,28] The FDA classifies calcipotriol as category C.[12]

Tazarotene, a topical retinoid, has insignificant systemic absorption.[6,12,29] Nevertheless, its risks for the developing foetus are still unknown due to limited data in humans.[6] Current recommendations are that its use is contraindicated during pregnancy until more data are available.[6,30] The FDA assigned this drug as category X for pregnancy.[12,14]

Finally, coal tar has been reported to be associated with spontaneous abortions, congenital disorders, and teratogenicity in animal studies and case reports.[6,31] Thus, although there are not enough studies linking the drug to

Table 2. Therapeutic options and relevant information regarding their safety in the treatment of psoriasis during pregnancy.

Therapeutic option	Relevant information
Topical therapy	
Moisturizers	- Well tolerated without significant adverse outcomes.
Corticosteroids	- No causal association between topical corticosteroids of all potencies and the risk of developing the vast majority of foetal abnormalities. - Probable association between potent-to-super-potent topical corticosteroids and low-birth weight (large amounts of cumulative exposure).
Calcineurin inhibitors (Tacrolimus)	- Limited data. Further data on topical use of this drug in pregnancy are required. - Topical use of calcineurin inhibitors is poorly associated with systemic absorption. - When in systemic circulation, tacrolimus can cross into the foetal circulation, causing low-birth weight, prematurity, transient neonatal hyperkalaemia, and renal dysfunction.
Anthralin/dithranol	- Limited data. Should be avoided.
Salicylic acid	- Limited data. Should be avoided. - If used, its application should be limited (low-to-moderate concentrations [<3%], avoid large amounts [>20 g per day], avoid use under occlusion). - Moderate or higher amounts can be systemically absorbed with deleterious effects to the foetus.
Vitamin D analogues (Calcipotriol)	- Limited data on humans. - Studies with animals show higher incidence of skeletal abnormalities. - Systemic absorption may occur with topical vitamin D analogues. Although the recommended topical dosage is considered safe, caution is required.
Topical retinoids (Tazarotene)	- Limited data on humans. Contraindicated during pregnancy until more data become available. - Despite the insignificant systemic absorption, the impact on foetus development in humans is still unknown.
Coal tar	- Limited data on humans. Avoid during the first trimester. Use with caution during second and third trimesters. - Associated with spontaneous abortions, congenital disorders, and teratogenicity in animal studies.
Phototherapy	
Narrowband ultraviolet-B (NB-UVB)/broadband UVB	- No foetal abnormalities or premature deliveries were associated with NB-UVB treatment. - Broadband UVB is a slightly less effective alternative but can be used if NB-UVB is not available. - There is a concern regarding the decrease of serum folate levels with UV light exposure. This deficiency rises the risk of foetal neural tube defects when associated with hyperthermia, and so, overheating must be avoided, especially during the first 28 days of gestation. Folic acid levels should be monitored during this treatment, along with adequate vitamin supplementation.
Psoralen plus UVA (PUVA)	- Should be avoided. - Few cases reported premature labour and foetal abnormalities. Psoralen has a theoretical risk of teratogenic and mutagenic effects, due to the inhibition of DNA synthesis and cell division.
Oral therapy	
Methotrexate	- Contraindicated during pregnancy, with an advisable 'washout' period of 3–6 months. - Maternal exposure associated with congenital malformations, with birth defects in several systems of the human body (i.e. gastrointestinal, cardiopulmonary, and central nervous systems), and with the development of the methotrexate syndrome (intrauterine growth retardation, deficient ossification of the calvarium, underdeveloped supraorbital ridges, small and low-set ears, limb anomalies, and developmental delays). - In animals, studies revealed an association between the drug and disturbances in spermiogenesis (chromosomal modifications and changes in the mobility of sperm). In humans, paternal exposure to the drug seems to have no impact on spermiogenesis, according to recent studies.

(*Continued*)

Table 2. (*Continued*)

Therapeutic option	Relevant information
Acitretin	- Contraindicated during pregnancy. Recommended to discontinue 2 years before conceiving a child. - Foetal exposure to acitretin may lead to a syndrome called 'retinoic acid embryopathy', which is characterized by malformations of the central nervous system and thymic structures as well as craniofacial and cardiac alterations.
Ciclosporin	- Limited data on pregnant women with psoriasis. - The association to low-birth weight and prematurity results from studies that enrolled transplant patients, that have a weaker state of health and use higher doses of the drug. Further studies are necessary to better understand the impact of the drug on pregnant patients with psoriasis. - Ciclosporin can cross the placental blood barrier and may achieve concentrations in the foetal circulation up to 50% of the maternal plasma concentration.
Apremilast	- Limited data on humans. Contraindicated during pregnancy. - In animals, apremilast was associated with abortion and low-birth weight in a dose-dependent manner.
Biological therapy	- Limited data.
a) TNF-α inhibitors	- Despite the limited available data, this type of inhibition seems to be a safe option during pregnancy.
- Etanercept, infliximab, adalimumab	- Despite the importance of TNF-α on embryogenesis and the transference of anti-TNF-α antibodies across the placenta, the available data point to low risk of teratogenic, embryotoxic, or fetotoxic effects with these drugs. - *Note:* The administration of live vaccines should be delayed until the age of 6–12 months old.
- Certolizumab pegol (CZP)	- No late active placental transfer due to its unique structure without the Fc portion. - The available data revealed no clear signs of foetal harm.
b) IL-12/23 inhibitors (Ustekinumab)	- Limited and contradictory information on pregnant women (studies reported an increase in the number of spontaneous abortions). Should be avoided until there is more data on safety of the drug in this type of patients.
c) IL-17 (secukinumab, ixekizumab, and brodalumab) and IL-23 (guselkumab and tildrakizumab) inhibitors	- Limited data on pregnant women. Should be avoided until there is more data on safety of the drug in this type of patients.

DNA, deoxyribonucleic acid; IL, interleukin; TNF-α, tumour necrosis factor alpha; UV, ultraviolet.

teratogenic effects in humans, coal tar should be avoided during the first trimester.[6] The application of the drug during the second and third trimesters should be limited to short periods of time (3–4 weeks).[6] There is no FDA pregnancy category for this drug.[12,14,20,31]

Phototherapy

Narrowband UVB/broadband UVB

Topical therapy might not be enough for moderate-to-severe psoriasis. Narrowband UVB (NB-UVB) is considered a first-line treatment when a systemic approach is required.[12] This therapy holds no FDA pregnancy category but has been successfully used during gestation.[12,32] No foetal abnormalities or premature deliveries were associated with NB-UVB treatment.[32] However, there are concerns regarding the decrease of serum folate levels with UV light exposure. This deficiency increases the risk of foetal neural tube defects when associated with hyperthermia and so, overheating must be avoided, especially during the first 28 days of gestation.[32,33] Folic acid levels should be monitored during this treatment, along with adequate vitamin supplementation.[6,9]

Broadband UVB is a slightly less effective alternative but can be used if NB-UVB is not available.[8]

Psoralen plus UVA

The safety of psoralen plus UVA (PUVA) on pregnant women has not been completely clarified yet, with few cases reported of premature labour and foetal abnormalities.[6] This drug is listed as FDA pregnancy category C. Psoralen, which is given orally to patients to increase the reactivity of the skin to UVA, has a theoretical risk of teratogenic and mutagenic effects, due to DNA synthesis and cell division inhibition. For this reason, PUVA should be avoided during pregnancy.[12]

Oral systemic therapy

Methotrexate

The FDA classifies methotrexate as category X.[6,12] It is absolutely contraindicated during pregnancy or in those planning pregnancy as this agent has been proven to be abortifacient, teratogenic, and mutagenic.[20] Discontinuation of methotrexate is recommended 3–6 months before conception because a 'washout' period is advisable.[34]

Studies developed with animals have revealed that methotrexate could cause disturbances in spermiogenesis, such as chromosomal modifications and changes in the mobility of sperm.[35] These data led to the insertion of a recommendation to discontinue the drug in men 3 months before conception. However, in humans, the available data seem to demonstrate that there is no impact of the drug on spermatogenesis.[35,36] Further studies are required to better understand the impact of the drug on men and pregnancy outcomes.

Maternal exposure to methotrexate is associated with congenital malformations, with birth defects in several systems of the human body (i.e. gastrointestinal, cardiopulmonary, and central nervous systems) which can even include the methotrexate syndrome. This syndrome is characterized by intrauterine growth retardation, deficient ossification of the calvarium, underdeveloped supraorbital ridges, small and low-set ears, limb anomalies, and developmental delays.[34,37]

Acitretin

The teratogenic risk of using a second-generation retinoid such as acitretin during pregnancy is considered very high, mainly during the first trimester of pregnancy, a period of higher risk of spontaneous abortion or congenital malformations.[38] Based on animal and human studies, this drug is listed as a category X by FDA.[12] It is contraindicated in childbearing women.[12,30]

Foetal exposure to acitretin may lead to a syndrome called 'retinoic acid embryopathy', which is characterized by malformations of the central nervous system and thymic structures, as well as craniofacial and cardiac alterations.[38] It is recommended to discontinue acitretin 2 years before conceiving a child. Thus, acitretin is an impractical therapy for most women considering pregnancy.[11]

Ciclosporin

Ciclosporin, an immunosuppressive drug, can cross the placental blood barrier and may reach concentrations in the foetal circulation up to 50% of the maternal plasma concentration.[39] Contradicting possible expectations, there are no reports of teratogenic effects in humans, with results showing that there is a similar risk of congenital anomalies and foetal loss compared to the general population.[12,40] For this reason, ciclosporin is considered by the FDA as category C.[12,41]

Nevertheless, there are few studies amongst pregnant patients with psoriasis.[6,12,41] Most information comes from patients who required transplantation. As the health status of these patients, who were treated with higher doses of ciclosporin than patients with psoriasis, may influence the findings shown in currently available data, the association to low birth weight and prematurity cannot be directly correlated with the use of ciclosporin.[6,12] Further studies are necessary to better understand the impact of the drug on pregnant patients with psoriasis.

Apremilast

At present, there are no human data regarding the use of apremilast, a small molecule that selectively inhibits phosphodiesterase-4, during pregnancy.[6,9] However, this drug has led to dose-related abortions and low birth weight in animals.[6] Currently, apremilast is contraindicated in pregnancy. It is listed by FDA as category C.[6,14]

Biological therapy

Due to their condition and underlying ethical reasons, pregnant patients with psoriasis are usually excluded from clinical trials. Thus, there is an obvious fault in large and controlled studies concerning TNF-α inhibitors and newer biologic agents, such as IL-12/23 inhibitor (ustekinumab), IL-17 inhibitors (secukinumab, ixekizumab, brodalumab), and IL-23 inhibitors (tildrakizumab and guselkumab).[10,42,43]

Most monoclonal biologic agents behave like maternal antibodies, but they do not cross the placenta in an equal way.[6] On choosing biological therapy during pregnancy, it should be kept in mind that the immunosuppression can be induced in both the mother and the foetus. In early pregnancy, the possibility of teratogenicity and foetus malformations must also be considered. Particularly for the foetus, one should keep in mind not only the possibility of immunosuppression but also the possible influence on the immune system development, in which the critical period is considered to be from the third trimester to 6 months old as a neonate.[6]

Most data on biological therapy come from animals, small retrospective studies, case reports or, most recently, from surveillance registries pointing outcomes from cases of pregnant women under treatment with biological agents.[42–45] Despite the risk of bias that these registries might suffer and the absence of well-controlled clinical trials, an increasing amount of literature suggests that biologic agents can be used for the treatment of psoriasis during pregnancy.[43,44,46]

TNF-α inhibitors

TNF-α inhibitors are the biologic agents most frequently used to treat immune-mediated diseases such as rheumatoid arthritis and inflammatory bowel disease. So, most data on their use in pregnancy come from rheumatology and gastroenterology literature.[42,44,46,47]

Maternal IgG antibodies can cross the placenta by simple diffusion. However, active transport of these immunoglobulins can be established via Fc receptors on the syncytiotrophoblast, which begins in the second trimester of pregnancy and rapidly increases over the third trimester.[14]

The transference of anti-TNF-α antibodies across the placenta occurs through binding between the Fc-region and neonatal Fc receptor; thus, a potential foetal or neonatal consequence exists.[48,49]

Conflicting data about the use of anti-TNF-α drugs have been published, and the available information is still limited.[42,43,50,51]

TNF-α may help to prevent structural anomalies during embryogenesis.[50,52] Obviously, this concept raised concerns about the impact of TNF-α inhibitors on the foetus.[50] However, regarding the use of etanercept, infliximab, and adalimumab, no substantial differences were found in the number of miscarriages, live-born infants, or congenital defects when compared with the general population.[50] Thus, these drugs are considered pregnancy category B by the FDA.[14]

Unintended exposure to etanercept and infliximab is considered to be low risk for pregnancy, at least from conception to the second trimester of pregnancy, and adalimumab has no data pointing teratogenic, embryotoxic, or fetotoxic effects.[6,14,43,44,46]

One issue with major importance is that live vaccines, such as MMR (against measles, mumps, and rubella), oral polio, rotavirus, and BCG (with Bacillus Calmette–Guérin), must be administrated with extreme caution to neonates exposed to TNF-α inhibitors during pregnancy.[6] In fact, a fatal case has been reported of a child from disseminated Bacillus Calmette–Guérin after administration of BCG at 3 months old whose mother received infliximab during pregnancy.[53] The current recommendation is to delay the administration of live vaccines until the age of 6–12 months.[6]

Certolizumab pegol (CZP) is the most recent anti-TNF-α drug receiving approval in Europe and the United States of America for the treatment of psoriasis and psoriatic arthritis.[54,55] Due to its unique structure without the Fc portion, which distinguishes CZP from other anti-TNFs, this drug has no late active placental transfer.[48] In fact, data from pregnancies with exposure to CZP showed no clear signs of foetal harm.[42,43,54] This can be explained by the fact that IgG is the only antibody that can cross the placental barrier between mother and the foetus by a specific Fc portion.[48,56] Without this portion, CZP is expected to cause lower foetal exposure when compared with other anti-TNFs, as its transference throughout the placenta barrier is compromised.[48,56]

An update on the pharmacovigilance database of pregnancy outcomes has been performed by Clowse and colleagues[54] on women affected by chronic inflammatory diseases. Although this study was not specifically on psoriasis, it is the most recent and largest cohort of pregnant women exposed to an anti-TNF-α drug. Considering the outcomes available for CZP, the large majority were live births (85.3%), with no suggestion of teratogenic effects or increased risk of foetal death, when compared to the general population. Indeed, most of these pregnancies were exposed to CZP during the first trimester and it was not found to have any link with major congenital malformations. This information is in accordance with other prospective studies.[50,56]

A prospective study named CRIB that evaluated the exposure of pregnant women to CZP during the third trimester concluded that there was none-to-minimal placental transfer of this drug to their infants.[56]

Although further studies are needed, CZP seems to be a safe solution during pregnancy when control of the disease activity is needed.[48,56]

IL-12/23 inhibitors

Ustekinumab acts by blocking the effect of both IL-12 and IL-23 through the inhibition of their shared receptor p-40 subunit. Ustekinumab could be transferred to the foetus in a modest way until the late second or even the early third trimester.[9]

Animal studies report no adverse effects for the foetus or offspring after exposure to ustekinumab.[12,14] However, there is limited and contradictory data on humans.[43] A few studies with pregnant women reported an increase in the number of spontaneous abortions.[43]

This drug is considered as category B by the FDA.[14] However, as data on its use during pregnancy is limited, ustekinumab should be avoided for now. As the median half-life is 21 days, the washout period for ustekinumab is 105 days (15 weeks).[6]

IL-17 and IL-23 inhibitors

Secukinumab (FDA pregnancy category B) and ixekizumab (no FDA category assigned) target IL-17A, whilst brodalumab targets IL-17RA (no FDA category assigned).[12] Guselkumab and tildrakizumab are selective IL-23 inhibitors (no FDA category assigned).

There is almost no data on the safety of these agents on pregnant women to date.[6,12,43]

The Novartis global safety database allowed the analysis of the outcomes of pregnancies with maternal or paternal exposure to secukinumab (from a clinical trial or postmarketing surveillance).[57] There were 292 pregnancies reported and no safety signals were identified regarding spontaneous abortions or congenital malformations.[57] Similarly, the outcomes of 58 pregnancies exposed to ixekizumab did not show differences when compared with US epidemiologic and Psoriasis Longitudinal Assessment and Registry (PSOLAR) data.[58] However, given the limited exposure reported to date, treatment with these biological agents should be avoided during pregnancy for now.[6,12,43]

Discussion

Pregnancy in a woman with psoriasis raises concerns about the impact of maternal psoriasis on foetal development, the impact of drug therapies on foetus health and the effects of pregnancy on psoriasis severity. Most women experience an

improvement of the disease, but an exacerbation of symptoms may occur.

Given the current literature, amongst the treatment options for psoriasis during pregnancy, topical therapies should be preferred over systemic therapies for mild disease. Emollients and moisturizers should be used liberally. Mild-to-moderate topical corticosteroids are the first-line treatment. In patients with moderate-to-severe disease, phototherapy with NV-UVB is the first-line treatment during pregnancy. Still, patients who cannot be managed effectively with topical therapies and phototherapy may require systemic therapy to achieve disease control. TNF-α inhibitors appear to be the best options considering the growing evidence of no teratogenic, embryotoxic, or foetotoxic effects of these drugs. CZP is probably the safest choice considering the absence or minimal placental transfer in comparison with other anti-TNF-α options.

Despite the recent data with no safety signs in pregnancies exposed to secukinumab and ixekizumab, these drugs should be avoided until more information is available.

The fact that there is a lack of data on the impact of the different treatment options during pregnancy, which occurs due to the ethical restrictions of conducting clinical trials in this type of patients, limits the possibility of drawing conclusions as to what will be the safest solutions for treating psoriasis in pregnant women. Future larger clinical trials or even real-world information through smaller studies and case reports involving childbearing women will be extremely important, especially data regarding the use of biologic agents, which are currently gaining importance in the armamentarium of psoriasis.

Conclusion

Women with psoriasis should plan a pregnancy when they are in remission and off medication or taking the minimum effective dose of medications that have the best foetal safety profiles. This situation is often unrealistic and there is a need for an effective and safe treatment option during pregnancy in women with psoriasis. Given the current literature, if patients cannot be managed successfully with topical therapies and phototherapy, then systemic therapy with anti-TNF-α drugs may be considered, with CZP positioning itself as the likely safest option considering an absent or minimal placental transfer of this drug. The recent findings regarding CZP may fulfil an unmet need of a systemic drug to use in fertile age women with psoriasis, without concerns about foetal adverse outcomes. Future studies will be extremely important to draw further conclusions about the impact of the different therapeutic options on the treatment of psoriasis during pregnancy.

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