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Managing Psoriasis during Pregnancy

Clara Liliana Soares Ferreira

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Managing Psoriasis during Pregnancy

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Discente: Clara Liliana Soares Ferreira

- Titular de Licenciatura em Enfermagem;

- Estudante do 6º ano profissionalizante do Mestrado Integrado em Medicina, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

- Nº aluno: 200504338

- Email: clarasoaresf@gmail.com

Orientador: Professor Doutor Tiago da Costa Ferreira Torres

- Grau académico: Licenciado em Medicina e Doutorado em Ciências Médicas

- Título profissional: Especialista em Dermatologia e Venereologia; Assistente Hospitalar no Centro Hospitalar e Universitário do Porto

- Afiliação: Instituto de Ciências Biomédicas de Abel Salazar, Rua de Jorge Viterbo, n.228, 4050-313 Porto

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Managing Psoriasis during Pregnancy

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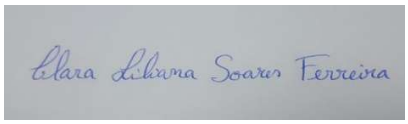

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(Clara Liliana Soares Ferreira)

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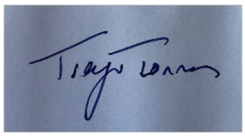

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(Professor Doutor Tiago da Costa Ferreira Torres)

Porto, 1 de junho de 2018

DEDICATION

Aos que, com clarividência e contra todas as vicissitudes da vida, continuam a

“amar pelos dois”

“Nada do que vivemos tem sentido se não tocarmos o coração das pessoas”

Cora Coralina

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À minha família que, para além de me ter dado a conhecer o significado de "amor incondicional", sempre me incentivou a continuar um percurso de procura constante de sabedoria. Em especial aos meus pais e irmã, obrigada não só por apoiarem o meu esforço, mas por fazerem também parte dele… não há palavras que cheguem para vos agradecer! Em particular, obrigada avó Carolina Gonçalves, o maior "tesouro" que eu poderia encontrado na minha vida... espero que o teu mérito seja um dia reconhecido, e por isso te prometo desde já "espalhar o teu nome aos quatro ventos".

Ao meu marido que, mesmo passando pelas intempéries que "as doenças" nos podem fazer passar na vida, conseguiu ainda assim dar-me força e coragem para seguir em frente e continuar a empenhar toda a força no sentido de concluir o curso que, segundo diz, me irá permitir "ajudar tanta gente". Assim o farei…

A todos os amigos que, com entusiasmo e tenacidade, acompanharam o meu percurso e souberam sempre dar-me "as palavras certas no momento certo". Obrigada por me proporcionarem tantos momentos únicos que me enchem de motivos para sorrir! Obrigada por terem acreditado sempre, vocês sabem que são "a família que eu escolhi".

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RESUMO

A psoríase é uma doença sistémica com impacto considerável na qualidade de vida dos doentes afetados. O seu pico de incidência coincide com a idade reprodutiva da mulher e a gravidez acarreta questões desafiantes em relação ao seu tratamento. De facto, tanto a saúde da mãe como a do feto têm de ser tidas em linha de conta. Ao decidir sobre o tratamento para a psoríase da mulher grávida (ou que pretende engravidar) através do uso de terapia farmacológica, é importante ter-se consciência das opções disponíveis e as suas repercussões. Assim, nesta revisão sistemática, pretendemos explorar de que forma a psoríase pode ser farmacologicamente abordada durante a gravidez, bem como nos casos em que a mulher pondera engravidar, de acordo com a informação existente e os possíveis efeitos, quer para a mãe, quer para o feto.

Relativamente aos métodos, foi realizada uma pesquisa usando termos MeSH (Medical Subject Headings) relacionados com este assunto, em bases de dados como PubMed, MedLine, Cochrane e ScieLO. Foram considerados estudos em humanos e animais, sem limite de tempo estabelecido, mas dando preferência às publicações mais recentes.

A vasta pesquisa realizada permitiu-nos reconhecer que a abordagem da psoríase na gravidez constitui um verdadeiramente um desafio. Apesar de existirem várias terapias farmacológicas disponíveis para o tratamento da psoríase, desde terapias tópicas a biológicas, passando pela fototerapia e terapia sistémica, a gravidez encerra questões éticas de suma importância, pelo que uma abordagem farmacológica deverá ser bem ponderada. A informação existente em seres humanos é limitada, sendo necessária mais investigação nesta temática. Dentro das terapias biológicas, o certolizumab pegol (CZP) foi recentemente apontado como sendo um fármaco promissor durante a gravidez, uma vez que revelou não ter ou ter mínima passagem através da barreira placentar.

ABSTRACT

Psoriasis is a systemic disease with considerable impact on the patient's quality of life. Its onset collides with women's reproductive frame time and pregnancy brings challenging concerns to its treatment. Indeed, both mother and fetus' health has to be considered. When choosing to treat pregnant women (or those who wish to conceive) affected by psoriasis with pharmacological therapy, it's important to be aware of the disposable options and their repercussions. Thus, on this systematic review we aim to explore how psoriasis can be pharmacologically managed during pregnancy, or in women considering childbearing, according to the current data available and possible effects for both mother and fetus.

As methods are concerned, we've pursued a research using MeSH (Medical Subject Headings) terms related with this matter, on data bases like PubMed, MedLine, Cochrane and ScieLO. We've considered studies in humans or in animals, with no limit in time established for the consulted articles. Preference was given to the most recent publications.

The extensive search performed allowed us to recognise that managing psoriasis during pregnancy is quite challenging. Although there are several pharmacological therapies available to treat psoriasis, from topical to biological therapies, passing through phototherapy and systemic therapy, pregnancy brings ethical concerns and a pharmacological approach must be well-thought-out. The data available in humans is limited and further investigation in this matter is needed. Within biological therapies, certolizumab pegol (CZP) has even been most recently pointed as a possible promising approach during pregnancy as this drug has shown no or minimal placental absorption.

KEYWORDS: Dermatologic agents/therapeutic use; Immunosuppressive agents/therapeutic use; Pregnancy/ Pregnancy complications/therapy; Psoriais; Psoriasis/treatment

INDEX

0- INTRODUCTION

Despite being recognised by its typical cutaneous symptoms, psoriasis consists in a systemic disease with complex pathomecanisms, on which environmental, genetic and immunologic factors play an influence.[1,2,3] This disease is epidemically and socially important as it affects 2.5% of the population[1], possibly leading to comorbidities and bringing major impact on the quality of life of the affected patients.[4, 5, 6]

The onset of psoriasis collides with women's reproductive years.[7] Thus, besides the expected endocrine and immunological changes during pregnancy, psoriasis brings a greater challenge for the maternal body.[8, 9] Considering that the course of the disease is quite unpredictable during pregnancy, a proper management of this stage of life must be wisely weighted, as both mother and the fetus must be considered.[5]

As it is difficult to achieve a balance between the advantages and disadvantages that the several therapeutic approaches might lead in the context of psoriasis, in this review we will present: the pathogenesis of psoriasis; its clinical features and therapeutical options available to treat psoriasis and its influence on pregnancy.

1-PSORIASIS

Affecting around 2,5% of the population worldwide, psoriasis is broadly recognised by its cutaneous features, since it's commonly identified by the emergence, on the skin, of papules and plaques covered with silvery scales.[1,2] Nevertheless, the hypothesis that psoriasis is a disease restricted to the skin was turned away by the identification of complex mechanisms involved in its etiopathogenesis which allowed to define psoriasis as a chronic, inflammatory and systemic disease.[1,2,3,7]

Psoriasis is influenced by environmental, genetical and immunological factors, and the spread of symptoms that go along with this disease can be large.[1, 2, 3, 4] Psoriasis may also be accompanied by comorbidities characterized by chronic inflammation of different degrees.[4,10] In fact, patients with psoriasis are under a higher risk of developing arthritis (which affects up to 40% of the patients), cardiovascular disturbances, metabolic syndrome, diabetes, inflammatory bowel diseases (like Crohn's disease), and other complications.[3,4,10,11,12,13] Thus, there's an impairment on the physical and psychosocial functions of these patients which leads us to consider that psoriasis has a negative impact on their quality of life and potentially on their long-term survival.[5, 6,13]

There are five subtypes of psoriasis described: vulgaris (plaque-type psoriasis), guttate psoriasis, inverse psoriasis, pustular psoriasis (either localized or generalized) and erythrodermic psoriasis.[14,15]

Classically, histological findings consist in acanthosis, hyperkeratosis, parakeratosis and expansion of epidermal rete ridges.[14,16] There is also an additional number of contorted and leaky vessels and an increased inflammatory cell infiltrate in the stratum corneum and epidermis (Munro's microabscesses and Kogoj pustules).[4,14,16] Therefore, a crosstalk between hyperproliferative keratinocytes, neutrophils, mast cells, dendritic cells and T cells induces inflammatory and pro-proliferative circuits, which leads to the development of psoriatic lesions.[14,17]

The involvement of the immune system in psoriasis is widely accepted.[18,19] An accurate characterization of the immune pathways underlying the psoriatic phenotype allowed the IL-23/IL-17 axis to be considered the main immune pathway in psoriasis pathogenesis.[17] Several factors induce the activation of mDCs (myeloid dendritic cells) with consequent IL-23 production. Indeed, keratinocytes arrange TSLP; fibroblasts produce TNF-α and IL6; pDCs (plasmacytoid dendritic cells) yield IFN-α, and natural killer T cells launch TNF-α and IFN-γ, which causes IL-23 to produce IL-20, nitric oxide and TNF-α.[20] Therefore, IL-23

stimulates specially T cell subsets (like T 17 and T 22) but also mast cells, neutrophils, and ILC3, leading to the secretion of IL-17 and IL-22.[17,20] High levels of IL-17 are expressed in lesioned psoriatic skin. Keratinocytes respond to IL-17 producing AMPs, chemokines (like CCL20, and CXCLs) and proinflammatory cytokines. CCL20 drives IL-17 to recruit IL-17+ T cell subtypes (Tc17, Th17 and γδ T cells) and mature mCDs.[17,20]. IL17 can also stimulate autoantigen production and neutrophil recruitment and survival.[17,21]Apart from the IL-23/IL-17 axis, strong evidence also suggests the contribution of multiple T-cell subsets (Tc1, Th1, Th9, Th21 and Th22) on the establishment of psoriasis.[22-25] Without undervaluing fibroblasts and endothelial cells role, the most preponderant tissue response is attributed to keratinocytes.[17,20] T-cell cytokines are responsible for acanthosis, as they induce proliferation and activation of keratinocytes, leading to the production of chemokines and other pro-inflammatory molecules (like IL-1β, IL-6, TNF-α and anti-microbial peptides), which amplifies immune cell recruitment and sustains inflammation and lesion in the skin.[12,17,26]

2-PSORIASIS AND PREGNANCY

The first symptoms of psoriasis usually occur between the second and the fourth decades of life and the diagnose is established, in average, at the age of 28.[7,27] So, the onset of the disease collides with women's reproductive years, pointing out that it is not uncommon to see psoriasis in pregnant women.[7,27-29] Thus, this stage of life is enhanced by the creation or maintenance of relationships.[30] So, besides the psychological burden possibly present in women diagnosed with psoriasis, it's important to reveal that this disease may also bring negative consequences for their partners.[31-34] Indeed, they also might feel their quality of life being questioned, as psoriasis might bring negative impact on the couple's relationship.[30,31] When considering pregnancy, couples should so be aware of the possible consequences both for mother s for the fetus about the implications of this disease and it's treatment options.[5,35,36]

Pregnancy entails an inimitable challenge for the maternal organism, as it involves remarkable endocrine and immunological changes.[8,9] The course of psoriasis during pregnancy is quite unpredictable.[5] Most women experience an improvement of their symptoms, and some even keep a steady state, but there are cases where there's an exacerbation of the disease.[5,27,36,37]

The impact of maternal psoriasis on the developing fetus is an aspect of great concern.[38] Studies pointed several adverse fetal outcomes, like spontaneous abortion, prematurity, macrosomia, disturbances related to weight (from large-for-gestational age to low birth weight) and a higher need for caesarean delivery. However, these associations were inconsistent among these studies, resembling that further investigation in this area is needed.[38]

The fact that severe disease may have a negative impact on both mother and fetus, highlights the importance of measuring equally the risks of treating or not treating psoriasis.[35]

3- MANAGING PSORIASIS DURING PREGNANCY

3.1- GENERAL CONSIDERATIONS

The first trimester matches the pregnancy's period with the highest chance of teratogenicity induced by drugs.[35] However, even when under treatments with eventual teratogenic effects, couples' compliance with pregnancy prevention is considerably poor.[35] Counselling prior to pregnancy is then an aspect of major importance as it provides not only education but also the timely decision on the most adequate therapeutic regimen having in view the possibility of pregnancy.[35,39] Also, in order to minimize possible flares of psoriasis during pregnancy, the ideal should be, if conceivable, to optimize the control or even to induce remission of the disease before conception.[29]

During pregnancy, the decision of treating psoriasis and how to manage the treatment options demands a careful thought, as both mother and the fetus' health must be considered.[5,40] The goal is to reach the best possible disease control, but it must be taken into account not only the extent of the disease on the affected pregnant women, but also the principal of not affecting the fetus in an undesired way.[5,41] However, due to obvious ethical constraints of performing clinical trials on pregnant women, there is limited data on this matter.[5] Most information comes from inadvertent fetal exposure due to treatments for psoriasis on women who were unaware of their pregnancy.[40,41]

In pregnant women with mild psoriasis or in those experiencing improvement of the disease during pregnancy, discontinuation of medication can be an option. However, this might not be the best choice for those experiencing severe psoriasis. So, it's mandatory to acknowledge the risks for pregnancy for each kind of treatment available.[40,41]

Concerns on the use of medication during pregnancy were highly enhanced since the 1960s, when thalidomide showed deleterious effects on the fetus.[42] Consequently, further investigation on drugs with teratogenic potential has been pursued and heightened regulation has been placed by governmental agencies.[43] Further data on animals and humans has been presented and in order to summarize the information obtained, classification systems have been established in order to help health professionals.[44]

A source of information on safety on using certain drugs during pregnancy is given by United States Food and Drug Administration (FDA). This system emerged in 1979 and was based in the classification of drugs into one of five letter system: A, B, C, D and X. [44,45] Each category relies on animal studies, human and data and information of risk of adverse effects against potential benefits of the drug, as listed in the following table (table I):[45]

A	Controlled clinical trials in females failed to show a risk to the fetus in the first trimester, and the possibility of harm to the fetus appears remote
B	Either animal studies did not show a risk to the fetus and no controlled human studies are available, or animal studies showed an adverse effect on the fetus but well-controlled clinical trials in pregnant females have failed to demonstrate a risk to the fetus
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 fetal risk exists in humans, but benefits in certain situations may justify the use of the drug despite its risks (e.g., 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 fetal abnormalities or there is evidence in humans of fetal risk, or both, and the risk outweighs any possible benefit

Table I - US-FDA pregnancy risk category definitions.[45]

To guide treatment of psoriasis during pregnancy, this categorization into letters has been helpful in clinical practise as replacing markers of risk stratification.[46] However, this system has proven to be often confusing, being overly simplistic and a limited way to reflect the available information.[44,47] So, using this system may lead to false assumptions about drugs based on their category.[44] According to this, in 2015 FDA introduced a new Pregnancy and Lactation Labelling Rule (PLLR), which replaces the letter rating system by narrative-based labelling requirements.[46,48,49] So, the application of this new system has been done by phases for existing medications, but drugs which have been approved after June of 2015 must necessarily fulfil the new PLLR.[43,49] For these drugs, it won't be attributed a safety category as they were replaced with individualized narrative summary of each drug.[49]

With the establishment of PLLR being so recent, at the present moment there are on the market therapeutics which are still attached to the previous categorization system, along with other drugs that already follow the new system given by PLLR.[45] Taking these aspects in consideration, on this review, reference to FDA categorization system will be made, if applicable, as well as other important data existing on use for each therapeutic.

Drugs will then be approached in this review according to their profile in terms of their adverse effects on pregnancy.

3.2- TOPICAL THERAPIES

The first line treatment options during pregnancy are topical therapies.[29,39,50] When used judiciously, there is no substantial systemic absorption, and levels high enough to cause adverse effects on the fetus won't be reached. However, overdose increases the risk of teratogenicity.[41]

Provided that the disease is limited, priority should be given to emollients and moisturizers as they are well tolerated, lacking significant adverse outcomes.[50]

Topical corticosteroids are known as the pillars of dermatotherapeutics.[51,52] When used appropriately (with the least potency required and judicious monitorization of duration and amount of application), they are assumed as safe for childbearing women.[51,53] FDA classifies topical corticosteroids as category C and although there is no risk of any fetal abnormality, it's stated that preference should be given to mild to moderate potency topical corticosteroids.[5,51,53] Potent or super potent topical corticosteroids should be used as second-line therapy as the current evidence points they are associated to a higher likelihood of low birth weight, particularly for large amounts. On these cases, meticulous obstetric care is mandatory.[51,53]

Topical calcineurin inhibitors like tracolimus are occasionally applied on small areas of sensitive skin on intertriginous areas (for example: genitals and face).[5,50] It is stated that, systemically, tracolimus can cross into the fetal circulation in humans and it has been related to low birth weight, prematurity, transient neonatal hyperkalaemia and renal dysfunction.[54-60] On its hand, topical use of calcineurin inhibitors is poorly associated with systemic absorption and so this application route is expected to be safe.[35,61,62] However, further information on topical use of this drug in pregnancy is required and so FDA classifies topical calcineurin inhibitors as category C.[5,35]

Within topical agents, anthralin (or dithranol)'s use is not currently approved during pregnancy, as there's not enough data concerning humans or animals.[35,50] FDA has assigned category C for this drug and it's pointed that it's use must be stopped 4 weeks before conception.[35,63]

There is also limited data regarding the use of salicylic acid during pregnancy and FDA assigned this drug as pregnancy category C.[35,50] However, it is recognised that moderate

amounts or higher concentrations can be absorbed systemically and there are studies pointing effects due to prenatal exposure.[64-66] Therefore, their use must be dodged.[35]

Systemic absorption may also occur on using calcipotriol, which is an analogue of vitamin D3.[5,41,67,68] There are no studies in humans reporting teratogen effects during pregnancy.[5,50,61,69] However, there are animal studies showing a higher incidence of sketal abnormalities and incomplete ossification of forelimb phalanges and pubic bones related to the administration of calcipotriol.[35] So, despite topical use of the recommended dosage is considered safe, caution is required, as there is no human data available at the moment.[5,50,61,69] FDA classifies calcipotriol as category C.[5]

On its hand, tazarotene, a topical retinoid, has trifling systemic absorption and combination with this drug may improve efficacy on treating psoriatic lesions, diminishing safety and tolerability concerns.[5,35,52,70,71] Nevertheless, it's risks for the developing fetus are still unknown as there is limited human data.[35,72] So, their use must be avoided during pregnancy and FDA assigned this drug as category X for pregnancy.[5,32,43]

As far as coal tar is concerned, the number of cases described are low, but the reports of spontaneous abortions, congenital disorders and teratogenicity found in animal studies raise major concerns.[32,61] Thus, although there are not enough studies proving teratogenic effects in humans, coal tar is not recommended during pregnancy and has no FDA pregnancy category.[5,32,50,69,73]

3.3- PHOTOTHERAPY

3.3.1- UVB/Narrowband UVB

In the presence of moderate to severe psoriasis, topical therapy might not be enough.[74] Narrow-band ultraviolet B (NB-UVB) is regarded as a first-line treatment when a systemic approach is needed[5]. This therapy holds no FDA pregnancy category but has been successfully used in pregnancy.[5,74,75] Recurrence to NB-UVB has shown no fetal abnormalities and premature deliveries aren't documented so far.[74,75] However, there are concerns regarding the decreasing of serum folate levels with UV light exposure. This deficiency rises the risk of fetal neural tube defects with hyperthermia and so, overheating must be avoided, especially during the first 28 days of gestation.[49,74,75,76] Therefore, the importance of monitoring levels of folic acid during this treatment acquires greater relevance, along with proper supplementation with this vitamin.[35,77]

Broadband UVB is a slightly less effective alternative, but it can be used if NB-UVB is not available.[36]

3.3.2- Psoralen Plus UVA

To increase skin reactivity to ultraviolet A (UVA), psoralen is orally administrated to patients who are under treatment with this phototherapy. PUVA (psoralen plus UVA) hasn't revealed to be unsafe, however this drug is listed as FDA pregnancy category C.[5,78] As a matter of fact, psoralen has a theoretical risk of teratogenic and mutagenic effects, as when in presence of UVA this drug inhibits DNA synthesis and cell division.[78] This way, PUVA must be avoided during pregnancy.[5]

3.4- SYSTEMIC THERAPY

3.4.1- COMMON SYSTEMIC DRUGS/ ORAL SYSTEMIC THERAPY

3.4.1.1- Methotrexate

FDA classifies Methotrexate as category X, that is, it's absolutely contraindicated during pregnancy or in those planning pregnancy as this agent has proven to be abortifacient, teratogenic and mutagenic.[28,50,76] Discontinuation of methotrexate is actually recommended three months prior to conception as a "washout" period is advisable.[69,79] The importance of prenatal counselling is also highlighted by the association of this drug with disturbances in spermiogenesis which interfere with chromosomic and mobility alterations on the sperm. Maternal exposure during pregnancy to this drug has an association with congenital malformations, with birth defects in several systems such as central nervous system, gastrointestinal and cardiopulmonary,[80-82] which can even include the methotrexate syndrome.[83-87] 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.[82,88]

3.4.1.2- Acitretin

The risk of using acitretin, a second-generation retinoid, during pregnancy is considered very high.[32,76] This drug is listed as a category X by FDA due to its teratogenic effects being the first trimester of pregnancy the period of higher risk of spontaneous abortion or congenital malformations.[89]

Fetal exposure to acitretin may lead to a syndrome called "retinoic acid embryopathy", which is characterized by malformations of the central nervous system, thymic structures, and even craniofacial or cardiac alterations.[89-91]

It is recommended to discontinue acitretin 2 years before conceiving a child,[92,93] which makes acitretin an impractical therapy for most women who have reproductive purpose.[39]

3.4.1.3- Ciclosporin

Ciclosporin can cross the placental blood barrier and may achieve up to 50% of the maternal plasma concentration.[94] Contradicting possible expectations, there is no report of teratogenic effects in animals or humans and so ciclosporin is considered by FDA as category C.[5,28] Nevertheless, there are few studies among pregnant patients with psoriasis.[95] Most information comes from patients who needed transplantation and the association between the low birth weight and prematurity reported can't be directly linked to the use of this drug as the health status of these patients may play an influence in the results observed.[5]

3.4.1.4- Apremilast

At the present, there is no human data concerning the use of apremilast during pregnancy.[35,40] However, betake of this drug in animals has led to dose-related abortions and reduced birthweight.[35] This way, apremilast is currently contraindicated in pregnancy, being listed as pregnancy FDA category C.[35,43]

3.5-BIOLOGICAL THERAPY

Due to their condition and underlying ethical reasons, pregnant patients with psoriasis are usually excluded from clinical trials. This way, there is an obvious gap on large and controlled studies concerning TNF-alfa (TNF-α) inhibitors and newer biologic agents, such as IL-12/23 inhibitor (ustekinumab) and IL-17 inhibitors (like secukinumab and ixekinumab).[96]

Most monoclonal biologics behave like maternal antibodies, but they don't cross the placenta in an equal way.[35] On choosing biological therapy during pregnancy, it should be kept in mind the immunosuppression that can be induced on both mother and the fetus.[5] In early pregnancy, possibility of teratogenicity and malformations must also be considered. Particularly for the fetus, it should be regarded not only the possibility of immunosuppression but also the possible influence in the immune development, being the critical period from the third trimester up to 6 months of age as a neonate.[35]

Most data on biological therapy comes 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.[96] Despite the risk of bias that these registries might suffer and the absence of well-controlled trials, the increasing amount of literature suggests that biologic agents can be used for treating psoriasis during pregnancy.[96-98]

3.5.1- TNF-α INHIBITORS

Antibodies to tumor necrosis factor α (anti-TNF) are the most frequently biological agents used to treat inflammatory diseases like rheumatoid arthritis and inflammatory bowel disease.[96,99] So, most data of their use in pregnancy comes from rheumatology and gastroenterology literature.[96]

It's known that 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.[28,43]

The transference antibodies anti-TNF across the placenta is done by the binding between they're Fc-region to the neonatal Fc receptor and so their use may bring fetal or neonatal effects.[99,100] This way, use of anti-TNFs has to be well thought out during pregnancy.[99]

Unlike other anti-TNFs, certolizumab pegol lacks an Fc-region and for this reason this drug will be discussed separately on this review.[99]

3.5.1.1- Etanercept, Infliximab and adalimumab

Conflicting data about the use of anti-TNF drugs has been published and the present information available is still limited.[96] Even the relationship between each TNF-α inhibitor and the risk of malignancy is still in debate.[101]

Investigations point out that cytokine TNF-α may help preventing structural anomalies during embriogenisis.[101-103] Obviously, this concept raised concerns about the impact of TNF-α inhibitors on the fetus.[96] However, as far as etanercept, infliximab and adalimumab, are concerned, no substantial differences were found in the number of miscarriages, live-born infants or congenital defects when compared with the general population.[101] These drugs are considered pregnancy category B by FDA.[43]

Unintended exposure to etanercept and infliximab is considered a low risk at least from conception till the second trimester of pregnancy.[35,43,104] Adalimumab even has no data pointing teratogenic, embryotoxic or fetotoxic effects.[105]

One aspect with major importance is that live vaccines MMR (against measles, mumps and rubella), oral polio, rotavirus and BCG (with Bacillus Calmette–Guérin) should be administrated with extreme caution in cases where a fetal exposure to TNF-α inhibitors occurred.[35] There is even a case report verifying the death of a child from disseminated Bacillus Calmette–Guérin after administration of BCG at three months of age whose mother

received infliximab during pregnancy.[106] The current endorsement is to delay the administration of live vaccines until the age of 6 to 12 months old.[35]

On the maternal side, there's a fundamental concern to consider: the risk of reactivation of tuberculosis, especially in areas where this disease is endemic. It's known that TNF-α is important to the integrity of the granulomas moulded in prior infection, and so, every patient should go under tuberculosis screening before initiating TNF-α inhibitors.[101]

Approaching infliximab in a particular way, it's known that this drug can lead to an infusion reaction (characterized by esophageal atresia, tracheophageal fistula, anal atresia and vertebral, cardiac, renal and limb anomalies).[43] The probability of its occurrence can be reduced by co-treatment with methotrexate. However, as discussed previously on this review, methotrexate is contraindicated during pregnancy. Being so, women tend to choose stopping infliximab at this stage of life. For those women, disruption of this drug is counselled 50 days prior to conception.[35,101]

3.5.1.2- Certolizumab Pegol

Certolizumab pegol (CZP) is the most recent anti-TNF drug receiving approval in the Europe and the United States of America for the treatment of psoriatic arthritis.[107] Thanks to its unique structure without the FC portion, by which CZP is distinguished from other anti-TNFs, this drug is known by its lack of late active placental transfer.[99] Pointing an advantage of its use, pregnancies with exposure to certolizumab pegol haven't shown so far clear signs of fetal harm.[108] That can be explained with the fact that IgG is the only antibody that can cross the placental barrier between mother and the fetus by a specific FC portion. Without this portion, CZP is expected to cause lower fetal exposure when compared with other anti-TNFs, as it's transference throughout placenta barrier is compromised.[61]

According to this idea, an update on the pharmacovigilance database of pregnancy outcomes has been performed by Clowse et. al (2018) on women affected by chronic inflammatory diseases. Although this study wasn't elapsed specifically on psoriasis, it's importance relies on the fact that it's the most recent and also the largest cohort of pregnant women exposed to an anti-TNF drug, CZP. Considering the outcomes available from the use of this drug, the large majority were live births (85,3%), with no suggestion of teratogenic effects or increased risk of fetal death, when compared to the general population. Indeed, most of these pregnancies were exposed to certolizumab pegol during the first trimester and it wasn't found any link with major congenital malformations.[108] This information collides with other prospective studies.[104,109,110]

As the exposure of pregnant women to CZP during the third trimester is concerned, a prospective study named “CRIB” concluded there was no or minimal placental transfer of this drug to their infants.[111] Although further information is needed, this evidence points out that as well as what’s been described for the first trimester (when the organogenesis primarily takes place), there is a lack of fetal exposure in utero to CZP in the third trimester.[108,111] Despite further studies are lacking, treatment with CZP is recommended throughout pregnancy when control of disease activity is needed.[111,99] This drug is considered as pregnancy category B by FDA.[108]

3.5.2-IL-12/23 Antagonists

3.5.2.1- Ustekinumab

Ustekinumab acts by blocking IL22 and IL-23 cytokines.[40] Being a large molecule, this human monoclonal antibody is expected to be transferred to the fetus in a modest way until the late second or even until the early third trimesters.[40,61]

Animal studies report no adverse effects for the fetus or offspring after exposure to ustekinumab and this drug is considererd as category B by FDA.[43,112] However, there is limited data on humans and this way this drug should be discontinued during pregnancy.[5,35,61] Discontinuing this drug one year before conception is advised.[113]

3.5.3- IL-17 ANTAGONISTS

Secukinumab (FDA pregnancy category B) and Ixekinumab (no FDA category assigned), target cytokine IL-17.[5] More specifically, IL-17A is targeted by brodalumab (no FDA category assigned). Currently, there is no data on the safety of the use of these agents on pregnancy on humans.[5,35] This way, treatment with these biological agents should be avoided during pregnancy.[5,35]

4- DISCUSSION

The establishment of psoriasis has its incept between the second and the fourth decades of life, matching women's reproductive years.[7,25,29] Being known by its impact on the quality of life, psoriasis brings particularly to this stage of life a major concern: the patient's self-confidence.[114]

Being young adulthood characterized by the creation and/or maintenance of relationships with partners,[114] women with psoriasis often suffer from stigma and see themselves in a restrictive way of living.[34,114-117] Even for these women's partners, a negative influence in their quality of life is assumed as an existing reality[118]. So, in the occurrence or when considering pregnancy, a discussion taking in account the several options of pharmacological therapy acquires even further relevance.[114]

The available treatments for psoriasis must be adapted to each clinical case, as its course during pregnancy is unpredictable.[5] Most women experience an improvement of the disease, but an exacerbation of the symptoms may occur.[5, 28, 36, 53] The impact on the developing fetus is also a matter of great concern, as it can be affected not only by maternal's psoriasis but also by the pharmacological therapy disposable in the market.[35,38]

Therefore, we aimed with this review to search for the available data on the safety of drugs used to treat psoriasis and its effects during pregnancy. We've found it to be is rather challenging, as there are possible effects on both mother and fetus.[5,40,41] Furthermore, there is limited data regarding safety, during pregnancy, of the disposable medications.[5] As obvious, there are ethical constraints on performing clinical trials on pregnant patients and so most information comes from inadvertent fetal exposure or from animal studies.[5,40,41,119]

Limited data among humans urges from a rather plausible concern: inappropriate use of drugs may lead to excruciating consequences, as seen with use of thalidomide, back in the 1960s.[43] Its teratogenic effects were so remarkable that scientific community felt the need to regulate use of drugs during pregnancy.[43,119] So, sources of information on safety emerged as attempts to guide doctors when prescribing certain drugs.[119] One of that sources is FDA, and we've recurred not only to FDAs new labeling system but also to the previous five-letters categorization system, to allow a better view on the existing information available on the drugs approached in this review.[46,43,48,119]

Among the treatment options available for psoriasis during pregnancy, topical therapies are considered the first line therapies for psoriasis during pregnancy, as no substantial

absorption is expected to occur.[39,29,41,48,50] Emollients, moisturizers and corticosteroids should be given priority as they lack significant outcomes.[50-52] Because potent or super potent topical corticosteroids are more likely to cause low birth weight, preference should be given to mild to moderate corticosteroids.[5,50-53] As far as calcineurin inhibitors, salicylic acid and calcipotriol are concerned, their use must be dodged as further information on their use in humans is lacking.[5,35,61,50,69] Still in the category of topical agents, it is important to notice that anthralin, tazarotene and coal tar are not recommended during pregnancy. [5,35,43,50,61,71,69,73] On its hand, although there is no safety categorization by FDA to coal tar, the reports of teratogenic effects found in animals makes it a drug to avoid during pregnancy in humans.[5,35,50,69,73] As for anthralin and tazarotene, FDA assigns these drugs as pregnancy safety category X.[5,35,43,63].

When a systemic approach is needed, phototherapy with NV-UVB is regarded as first-line treatment for psoriasis during pregnancy,[7,50,75] as the only side effect documented so far is the diminishing of serum folate levels because of the UV exposure, that can be outdated by monitoring its levels and appropriate supplementation with this vitamin.[40,49,75-77] Otherwise, PUVA must be avoided because of its theoretical risk of teratogenic and mutagenic effects, holding a C category on the FDA categorization system for pregnancy.[5,78]

As systemic therapy is concerned, methotrexate and acitretin are listed as FDA pregnancy category X, being absolutely contraindicated during pregnancy as they are related to teratogenic effects.[25,50,76,89] Although apremilast holds a category C on FDA categorization system, it is also contraindicated during pregnancy because in animals this drug has led to abortions and reduced birthweight.[35,43] Otherwise, ciclosporin, FDA category C, emerges as possible alternative if a systemic approach is needed, as there are no reports of teratogenic effects in animals or humans.[5,25]

Most recently, a better understanding of the immune pathways involved in psoriasis allowed the development of biological agents which target increasingly specific cytokines related to psoriasis.[1] Examples of biological therapies are anti-TNFs (etanercept, infliximab, adalimumab and CZP), IL-12-23 inhibitor ustekinumab and IL-17- inhibitors (secukinumab and ixekinumab).[96]

Conflicting data has been published about anti-TNF drugs etanercept, infliximab and adalimumab (classified by FDA as B category for pregnancy safety) and further data is lacking.[43,96] However, unintended exposure to etanercept and infliximab, from conception and until the second trimester of pregnancy, is faced as a low risk for the fetus.[35,43,104] In the case of adalimumab, there is even no data pointing adverse effects for the fetus.[105]

Along with the approached anti-TNF drugs, ustekinumab also holds an FDA category B. Nevertheless, this human monoclonal antibody is expected to be transferred to the fetus in a modest way until the late second or even until the early third trimesters and so it's advised to be discontinued one year before conception.[40,61,113]

As IL-17 inhibitors secukinumab (FDA category B) and ixekinumab (no FDA categorization) are concerned, it's stated these drugs must be avoided during pregnancy due to lack of further safety information.[5,35] For brodalumab, which targets IL-17-A, it seems to be a promising ally for the treatment of psoriasis when combined to an anti-TNF drug, again, lacking further data on pregnant women.[120]

Thus, underlined with the use of biological therapy, the concept that immunosuppression can be induced on both mother and the fetus has been globally considered, and even a possible influence on the development of the fetus immune system is mentioned.[5,35] However, recent findings have shown that this risk might not be present or be minimal in the case of CZP, an anti-TNF drug, because of its lack of an FC-region in its structure. So, this drug is not expected to cross the placental barrier and there are no signs pointing harmful effects on the fetus, which is quite promising.[121-124] Studies relating more specifically the use of CZP in pregnant women are lacking.[122]

Overall, the increasing amount of literature is in favor of recurrence to biological therapies.[96,97,98] However, further investigation is needed and pregnant women, for ethical reasons, can't be a part of controlled trials, which can be rather challenging when choosing a pharmacological approach for psoriasis.[43]

5- CONCLUSIONS

The onset of psoriasis collides with women's reproductive years and brings a major impact for pregnant women and their partners.[7,25,28,29]

Facing psoriasis during pregnancy can be rather challenging as we must regard both mother and fetus' health.[5] So, we aimed to acknowledge how psoriasis can be managed during pregnancy. As approached, several studies have been pursued to evaluate the best disposable pharmacological therapies options for psoriasis when pregnancy occurs, or for those who wish to conceive.[35,38]

Pre-counselling before pregnancy would be the ideal situation in order to choose, in a more adequate way, the most appropriate drug for each clinical case. Furthermore, as seen in this review, certain drugs should be stopped even before conception.[35] However, we must keep in mind that only a few couples resort to medical counseling before pregnancy and usually the settings on the medication are done when women are already aware of their pregnancy.[35]

Nowadays, several pharmacological treatments are available to treat psoriasis: topical therapy, phototherapy, systemic therapy and biological therapy. The approach of each different therapeutic group pursued on this review enhanced that further data on this matter is lacking.

Recent researches on the psoriasis-signature cytokines that are underlying the establishment and worsening of psoriasis allowed a better understanding on the pathways on which different biological therapeutic might be helpful. A promising breaking point on the way pregnant women with psoriasis are treated might be on recent findings about CZP. This biological drug has sown no or minimal placental transfer and this aspect might lead to a new horizon on the reach of safer pharmacologic offers to fertile age women with psoriasis.

As a final comment, and given the limited data available, we stand out the importance of deeper studies on this matter, provided with the most adequate registries and data available in context of pregnancy in women with psoriasis. In this review we've attempted to do that recurring to the FDA categorization system for pregnancy. It was rather notorious in this review the importance of the new labeling system established by FDA since 2015. The old five-letter categorization system to which we have resorted for therapies available on the market before 2015 revealed to be, as expected, quite simplistic and contradictory. As an example, we've described drugs which belong to the same safety category for pregnancy,

but there are contradictory demandings on their use during pregnancy, which is quite confusing. This way, we conclude that the attempts of giving guidance for clinical practitioners have huge importance.

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