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Archives of Anatomy and Physiology

ISSN: 2640-7957 DOI: http://dx.doi.org/10.17352/aap

Review Article

# Interaction of psoriasis and pregnancy: Maternal and fetal outcomes

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**Received:** 15 February, 2020
**Accepted:** 11 March, 2020
**Published:** 13 March, 2020

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**Keywords:** Psoriasis; Pregnancy; Management; Maternal outcome; Fetal outcome

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## Abstract

Psoriasis is a chronic immune-mediated inflammatory disease that affects about 2%-4% of the population. Clinically typical erythemato-squamous papules and plaques of different sizes and shapes on the skin are characterized by the parallel appearance of epidermal hyperproliferation, inflammation and angioneogenesis. Although many factors are blamed in the etiology of psoriasis, genetic and environmental factors play a role in the pathogenesis of the disease. However, there may be fluctuations in psoriasis activity by hormonal changes and pregnancy. Overall, three out of every four psoriasis patients experience a change in the course of the disease during pregnancy. The proportion of those with improvement in the course of psoriasis is about twice as high as those with worsening. However, generalized pustular psoriasis of pregnancy seen in the last trimester of pregnancy can lead to serious maternal and neonatal morbidities and even mortality. On the other hand, some complications such as low birth weight, preterm birth, gestational diabetes, gestational hypertension, preeclampsia and emergency cesarean section have been reported more frequently in pregnant patients with severe psoriasis. Therefore, considering the adverse maternal and fetal outcomes of severe psoriasis and the fetal side effects of systemic psoriasis treatments, psoriasis in pregnant cases should be managed well by keeping the risk-benefit ratio in balance. In this article, the concerns and misconceptions of the patients with psoriasis about pregnancy and psoriasis interaction, pre-pregnancy counseling, the course of psoriasis during pregnancy, the pregnancy course in patients with psoriasis, and the management of psoriasis in pregnant women have been extensively reviewed, respectively.

## Abbreviations

PsA: Psoriatic Arthritis; Th: T Helper; IL: Interleukin; TNF-α: Tumor Necrosis Factor-Alpha

## Introduction

Psoriasis is a chronic immune-mediated inflammatory disease that affects 2%-4% of the world's population and is characterized by periods of remission and exacerbation. It can be seen as a wide clinical spectrum of various skin manifestations including erythemato-squamous papules, plaques, pustular lesions, palmoplantar hyperkeratosis and fissurations. Although lesions of different sizes ranging from a pinhead up to a diameter of 20 cm can be seen in any part of the body, it most commonly affects the knees, elbows, scalp, lumbosacral and genital regions. Psoriasis vulgaris is the most common clinical subtype. However, different clinical types such as guttate, erythrodermic, palmoplantar, inverse and pustular psoriasis (generalized or localized) may also appear alone or together. The diagnosis is easy if suspected, though rarely it may be hard to distinguish from other dermatosis. Eczema is a differential diagnosis of psoriasis, of which topical corticosteroids remains the mainstay of treatment. Besides typical skin involvement in psoriasis, significant deterioration of the nails and painful inflammatory joint involvement (psoriatic arthritis, PsA) can also be seen [1].

Genetic factors and environmental factors such as trauma, medications and infections are thought to play a role in the etiology of psoriasis [2,3]. There is a complex immunological reaction that results in epidermal hyperproliferation with abnormal keratinocyte differentiation. Following the activation of immune system elements such as keratinocytes and dendritic cells, there is a development of some functional T cell subpopulations such as T helper (Th) 1 and Th17, especially with the effect of the activation of T cells that migrate to the skin and certain cytokines (e.g., interleukin (IL) -12, IL-23). These lead to the secretion of pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α), IL-17 and IL-22. With the secretion of adhesion molecules and other mediators, they lead to an increase in the inflammatory process in psoriasis [4]. In addition, some comorbidities such as metabolic syndrome, cardiovascular disease, arthritis and inflammatory bowel disease accompany psoriasis, as evidence



**Citation:** Akarsu S (2020) Interaction of psoriasis and pregnancy: Maternal and fetal outcomes. Arch Anat Physiol 5(1): 001-008.
DOI: https://dx.doi.org/10.17352/aap.000013

that the underlying inflammatory process harms many organs [5,6]. Psoriasis management is very complex and challenging. The choice of treatment should be made individually based on various factors such as the patient's age, gender, clinical type and severity of psoriasis, the effect on the patient's quality of life, comorbidities and pregnancy status. The disease, which can exhibit variable clinical appearances and most commonly seen in plaque form, is mild in approximately 85% of the cases and can be controlled by topical treatments and phototherapy. On the other hand, moderate or severe psoriasis occurs in 15% of cases, requiring treatment with systemic agents and continuous follow-up, with comorbidities occurring more frequently [7].

About half of all patients with psoriasis are women, and in more than 75% of those cases the onset age of psoriasis is observed before the age of 40 years. In other words, the diagnosis of psoriasis (mean age: 28 years) and the onset of treatment coincide with the peak reproductive age (18-45 years) [1,8]. Additionally, accompanying diseases (obesity, hypertension, diabetes mellitus, depression, and other chronic inflammatory diseases such as inflammatory bowel disease and rheumatoid arthritis) were found to be associated with adverse pregnancy and birth outcomes in most patients with psoriasis [5]. Pregnancy is a unique physiological condition. It can progress with changes in many organs and systems, especially endocrine, vascular and respiratory systems. These physiological changes create favorable conditions for the growth and development of the fetus while preparing the mother for childbirth. The first trimester of pregnancy (the first 13 weeks) is the period of formation and development of the embryonic organs. During this period, the fetus is extremely sensitive to factors such as systemic diseases of the mother, medications, smoking and alcohol consumption. Therefore, special attention should be paid to this period as about half of the pregnancies are not planned and the risks of many drugs are especially high in the first trimester [9]. Otherwise, pre-pregnancy (pre-conception) counseling is mandatory in patients with a chronic disease such as psoriasis and possibly requiring long-term medical treatment [9,10].

The purpose of this paper is to review extensively the concerns and misconceptions of the patients with psoriasis about pregnancy and psoriasis interaction, pre-pregnancy counseling, the course of psoriasis during pregnancy, the pregnancy course in patients with psoriasis, and the management of psoriasis in pregnant and breastfeeding women. Some conflicting data are available from published literature on impact of psoriasis on pregnancy outcomes. In this article, in addition to review the current knowledge about this topic, more recent reviews, brief reports and case series are also included to assess the benefit-risk balance associated with psoriasis treatments and the course and outcome of pregnancy in women affected by psoriasis.

## Inadequate awareness and misconceptions about the interaction of psoriasis and pregnancy

### Psoriasis and pre-pregnancy period

Generally, impaired quality of life (such as unhappiness, stress, loneliness, stigmatization, decreased sexual activity) has been found to be more frequent in women with psoriasis as compared to men with psoriasis. Although it is not thought to affect fertility, pregnancy rates have been observed to be approximately 22% lower in women with psoriasis. Among the reasons for this, it has been suggested that many factors such as women's unwillingness to voluntarily, concerns about pregnancy and/or postpartum disease activity, fear of the effect of psoriasis treatments on pregnancy and baby, as well decreased closeness due to embarrassment and/or physical inability play a role [8,11].

According to a survey result in women of childbearing age with psoriasis (psoriasis: n= 367; PsA: n= 142) from the different countries (United States, Japan, Germany, France, Italy, Spain, and the United Kingdom), it was determined that 25% of the patients with psoriasis and more than half of the patients with PsA delayed the pregnancy decision. The main reason was reported to be concern for genetic transmission of the disease (psoriasis: 41%; PsA: 39%) [12]. Although much is still unknown in relation to the heredity and subsequent development of psoriasis; the risk of developing psoriasis in a newborn child is 50% if both parents have psoriasis, 16% if only one parent has psoriasis, and 16% if only one sibling has psoriasis when there is no psoriasis in the mother or father. In general, 40% of patients with psoriasis also have psoriasis disease in their 1st degree relatives. It is seen together in 70% in monozygotic twins and 30% in dizygotic twins. For reasons that have not yet been established, it was found that affected men have a higher risk of transferring psoriasis to their children [3,13-15].

As a result of a study conducted by the National Psoriasis Foundation in 141 women with psoriasis, it was determined that 88% of the patients received advice from the internet and 68% consulted the physician who provided psoriasis/PsA treatments for information about pregnancy planning. Only 7% of the interviews were initiated by their family physicians. Asking a specialist opinion before pregnancy from these women interviewing the family physicians (psoriasis: 46%; PsA: 53%) was lower in patients with psoriasis without arthritis (psoriasis: 39%; PsA: 71%). Only 43% of those receiving systemic medication before pregnancy used a contraception method. It was observed that 33% of patients were late in notifying the physician who provided psoriasis/PsA treatment and 20% did not even tell about their pregnancy. In 22% of mothers who had discontinued medications due to the pregnancy, it was recommended to wait for postpartum exacerbation to start treatment again [16].

### Psoriasis and pregnancy period

Murase et al. observed that pregnant women with psoriasis did not have information about the effect of treatment options on pregnancy (psoriasis: 31%; PsA: 40%). During pregnancy, patients were mostly referred to gynecology, only half of them were asked for dermatologist or rheumatologist consultations for psoriasis (for psoriasis: 46% dermatologist, 86% gynecologist; for PsA: 51% dermatologist, 61% rheumatologist, 70% gynecologist). A planned treatment was present in 64% of women with PsA and only 28% of women with psoriasis [12].



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DOI: https://dx.doi.org/10.17352/aap.000013

According to another research by the National Psoriasis Foundation, 65% of women with psoriasis were observed to cut off treatment in pregnancy. It was determined that 79% of these patients were afraid of the possible harm of the treatments to the baby, 40% of patients discontinued the treatment by their own decision, 47% of patients stopped the medication by the recommendation of the physician giving the treatment, 44% of them had an increase in the severity of psoriasis and in more than 65% of patients were found to have no plans for the control of psoriasis exacerbations during pregnancy [16].

### Psoriasis and postpartum period

Murase et al. highlighted that about a quarter of women who discontinued psoriasis treatments because of pregnancy were not informed about the possibility of postpartum exacerbation and it was not recommended to start treatment again during this period. It was observed that 75% of women with psoriasis and 65% of women with PsA breastfeed their babies. However, 44% of women with psoriasis and 78% of women with PsA felt obliged to choose between treatment and breastfeeding during lactation period. In addition, approximately a quarter of patients (psoriasis: 16%; PsA: 24%) did not know the effect of treatments on lactation [12].

## Psoriasis and pre-pregnancy counseling

Among the issues that need to be paid attention and information for pre-pregnancy awareness in patients with psoriasis; the risks of psoriasis disease and inadequate treatment on the mother and baby, the risks of specific psoriasis treatments for possible fetal defects, alternative drugs or non-pharmacological options for psoriasis, the lowest effective dose of treatment, considering the correct timing for the cessation of the drug at the highest risk period, early transition from oral contraception to barrier methods for birth control, postponing pregnancy until optimal disease control is achieved, as well as pre-pregnancy vaccination and immune control against rubella and varicella (chickenpox) before starting an immunomodulatory treatment should be evaluated comprehensively for the health of mother and baby [9,10,17]. All women also should be vaccinated against influenza during the flu season. Pertussis (*whooping cough*) booster that is given at 26-28 weeks for all pregnant women can also be offered to possible child-minders such as grandparents. In addition, live vaccines such as MMR (measles, mumps, rubella) and varicella vaccines should be avoided in people who are still receiving immunosuppressive therapy [9]. Pre-pregnancy counseling also offers the opportunity to discuss important aspects of other common risk factors, including maternal age, family history, general health and lifestyle health risks such as diet, weight, smoking, alcohol and illicit drug use [9,10].

## The course of psoriasis during pregnancy

There may be occasional fluctuations in psoriasis activity with hormonal changes and during pregnancy [18]. In a prospective study of 163.763 women (n= 1.253 psoriasis patients), a higher risk of psoriasis was found in women with irregular menstruation and surgical menopause. It was reported that the risk of psoriasis was lower among young women who had multiple births and had longer breastfeeding periods [19].

In multiple pregnancies, it was observed that the course of improvement or worsening of psoriasis in the first pregnancy has a similar tendency in each subsequent pregnancy. Most women experience improvement (32%-63%) or stabilization (21%) in psoriasis during pregnancy. In patients with psoriatic involvement in more than 10% of the body surface area, a reduction of more than 80% in lesions was determined between the first and third trimesters. However, exacerbation or stable high disease activity is observed in about a quarter of patients with psoriasis (psoriasis: ~23%; PsA: ~9%). Considering all patients with psoriasis, exacerbation is seen in 65% (40%-88%), stabilization in 25% and improvement in 10% in the postpartum period. The psoriatic body surface area doubles approximately between the 30th week of pregnancy and the 6th week of postpartum period. However, the increased body surface area values usually do not exceed the values of the first trimester, indicating that patients returned to their baseline condition [20]. Recent studies reported that exacerbations were observed in 70% of patients with PsA in the postpartum period, while improvement or remission was observed in approximately 80% during pregnancy [21-23].

Generalized pustular psoriasis of pregnancy, which has also been referred to as "impetigo herpetiformis", is a special medical condition characterized by fatal progression for both mothers and their babies when not treated. While most patients have a personal or familial history of psoriasis, some may not have. Hypoparathyroidism, hypocalcemia, stress, and infections can trigger the appearance of the disease. The disease usually begins in the early period of the third trimester of pregnancy. Although the occurrence of pustular lesions usually continues until birth, rare patients that persist after delivery have been reported. Sterile pustular lesions grouped on erythematous plaques usually begin from the axillar, inguinal or other flexural regions, progress towards the periphery and tend to dry in the center. The lesions spreading centrifugally and symmetrically towards the extremities are not seen on the face, palmar and plantar areas. As a result of excessive eroded, weeping and crusted lesions, vegetative plaques similar to pemphigus vegetans may develop. Lesions with itching or burning sensations are foul-smelling. They heal leaving red brown pigmentations. When tongue, buccal mucosa, and even the esophagus are affected, circinate lesions (circular or ringlike in shape) appear. Patients may experience fever, weakness, and even death due to cardiac and renal failure. Disease-related delirium, diarrhea, vomiting and tetany have been described. Inflammation markers such as erythrocyte sedimentation rate and white blood cell counts increase. Hypocalcemia, hypoalbuminemia, and iron deficiency anemia can also be detected. In severe cases that can turn into erythroderma, dangerous fluid and electrolyte imbalances, loss of thermoregulation in the skin, and the risk of secondary infection and sepsis occur. Additionally, intrauterine growth retardation, premature rupture of membrane, miscarriage, stillbirth and fetal anomalies may develop due to placental



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insufficiency in more long-standing and severe forms. Although pustular lesions usually regress with parturition, they frequently recur earlier in other pregnancies [24,25]. It can also be triggered by menstrual cycle changes and the use of oral contraceptives [26].

Although the cause of improvement in pregnancy and exacerbation in postpartum periods for Th-1-mediated autoimmune diseases such as psoriasis is uncertain, it is probably related to changes in cellular and humoral immunity that occur in the natural process of pregnancy. HLA-Cw*0602 positivity was determined genetically in patients with psoriasis who had remission during pregnancy. As it is known, maternal immunosuppression is required physiologically for the survival of fetal allograft in pregnancy. While there is a decrease in the number of CD3, CD4, CD8 and CD20 cells during pregnancy, an increase is determined in the number of CD4, CD20 and CD16 cells in the first month, and CD3 and CD56 in the fourth month of the postpartum period. Increased synthesis of asymmetric IgG antibodies also results in a successful pregnancy. Pregnancy-specific glycoproteins (PSG1, PSG6, PSG11) with immunomodulatory properties provide in vitro IL-6, IL-10 and TGF-β1 secretion while does not secrete IL-1β, TNF-α or IL-12 [27,28].

The altered endocrine environment in pregnancy is likely to down-regulate the immune-mediated inflammatory cascades of psoriasis. In the third trimester of pregnancy, progesterone is found 25 times and estradiol is 100 times higher than those who are not pregnant. While estrogen increase and increase in estrogen/progesterone ratio are associated with improvement in psoriasis, progesterone alone is not effective. Estrogen suppresses the production of IL-2 from active T cells in the peripheral blood and CD4+ T cells at the transcriptional level. The predominant estrogen is oestradiol, whereas estrogen secreted from the placenta only in pregnant women is oestriol. The decrease in psoriasis severity is associated with significant estradiol and partially significant estriol increase. Effects of estradiol on psoriasis are as follows; a- It triggers the production of Th2 anti-inflammatory cytokines (IL-4, IL-5, IL-10) while inhibiting pro-inflammatory Th1 and Th17 cytokines (IL-2, IFN-gamma, TNF-α and IL-17). b- It increases regulatory T cells, which provides tolerance to pregnancy with its immunosuppressive effect especially in the first trimester of pregnancy. Increased regulatory T cells, whose functions and numbers are normally low in psoriasis, lead to immune tolerance, and modulation of Th1 and Th17 cell activation. c- It stimulates the transformation of CD4+CD25- T cells into CD4+ CD25+ T cells, thereby increasing the expression of Foxp3 and IL-10. d- It reduces the production of free oxygen radicals and increases antioxidant enzyme gene expression. Thus, it contributes to the healing of psoriasis by reducing oxidative stress. e- Estrogen has a two-way effect on keratinocytes. It worsens psoriasis by stimulating keratinocyte proliferation while it improves psoriasis by regulating lipid content and structure of the stratum corneum, increasing skin barrier function and also reducing the production of keratinocyte chemokines (e.g., RANTES, MCP-15). Although progesterone is not as effective as estrogen, it produces a Th2 dominant immune response by stimulating a mediator protein (progesterone induced blocking factor) synthesis from lymphocytes and increasing the production of Th2 cytokines (IL-4, IL-5) [29]. Prolactin, human placental lactogen, human chorionic gonadotropin and especially glucocorticoids, which are constantly increasing during pregnancy, may also have significant immunosuppressive effects [28,30].

Postpartum exacerbations have been associated with a decrease in estrogen levels. In addition, the exacerbation of Th1-mediated autoimmune diseases such as psoriasis in postpartum period while improving during pregnancy is a reflection of the complexity in the cytokine network. Th2 cytokines (IL-4, IL-10, etc.) are more predominant during pregnancy, but Th1 cytokines (IL-2, TNF-α, etc.) predominate in the early postpartum period. [31,32]. Ex vivo monocytic IL-12 and TNF-α production levels in postpartum period are higher than the values in the third trimester. Moreover, the levels of serum 1.25-dihydroxyvitamin, urinary cortisol and norepinephrine excretions are lower in the postpartum period, which hormones suppress in vitro IL-12 and TNF-α production from monocytes/macrophages [28].

## Pregnancy course in patients with psoriasis

Pregnancy results are quite variable in women with psoriasis. Recently, Lambe et al. observed that women with psoriasis were younger at first birth and had longer interpregnancy intervals but did not differ in final parity in comparison to women without psoriasis [33]. Although there are some studies reporting preterm delivery, low birth weight and recurrent miscarriages, the results are contradictory [33-46]. In a systematic review of nine observational studies (six studies of good quality), there was no consistent evidence associated with an increased risk of adverse pregnancy outcomes in women with psoriasis [42]. Similarly, in a study using the *National Inpatient Sample (NIS)* database in the *United States* (2003-2011; 11.204 women with psoriasis/PsA), maternal psoriasis/PsA had no significant effect on maternal/fetal death. In addition, the prevalence of preterm delivery, premature rupture of membranes, postpartum hemorrhage and cesarean delivery are similar to the control group [46]. However, there are studies that determine the relationship between disease activity and pregnancy complications or negative pregnancy outcomes [33,39]. In a cohort study using prospective data from Denmark and Sweden (April 2007-December 2012; 8.097 babies born from mothers with psoriasis/PsA), the increased risk of gestational diabetes, gestational hypertension, preeclampsia and emergency cesarean section in women with psoriasis was higher in those with severe clinical variants. The risk of moderate preterm delivery (32-36weeks) and low birth weight were also found to be high. Women with PsA also had an increased risk of gestational hypertension and preeclampsia [39].

As it is known, preterm delivery, preeclampsia and unexplained recurrent miscarriages are more likely in autoimmune diseases (e.g., rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus) associated with an increase in Th17 cells and Th17/regulatory T cell ratio [31].



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DOI: https://dx.doi.org/10.17352/aap.000013

Systemic and placental vasculopathy occur also in psoriasis probably by immune dysfunction, proinflammatory cytokines and the effects of psoriasis on endothelial cells. Certain factors such as psoriasis severity, duration of psoriasis, maternal age and increased comorbidities (metabolic syndrome, diabetes, obesity, cardiovascular disease, hypertension, osteoporosis, depression/anxiety, smoking and alcohol consumption) may also contribute. Advanced gestational age, low prenatal vitamin intake, obesity and cigarette consumption has also been often found in pregnant women with psoriasis [8,9,42].

## Management of psoriasis during pre-conception, pregnancy and lactation period

According to synthesis of current literature, a treatment approach is recommended similar to the pregnancy and lactation period in women with psoriasis who are not using any contraceptive method at childbearing age and/or want to become pregnant. The patient should be told that approximately 10%-20% of all cases of plaque psoriasis may worsen during pregnancy. Similarly, 50% of pregnant women with psoriasis may experience an exacerbation of the psoriatic lesions within the first 6 weeks after birth [47]. It should not be forgotten that some potential problems may occur against psoriasis treatment agents during these periods. Especially when systemic treatment indication arises, potential risks should be explained and treatment should be started after obtaining patient consent. Particular attention should be paid to this period, as it is unpredictable when the conception will take place in an unprotected fertile female patient and the risks of many drugs are particularly high in the first trimester [8-10,17].

It is well known that any drug use during pregnancy is avoided because of concerns about possible side effects to the fetus. Drug studies on pregnant women cannot be carried out for ethical reasons. As a consequence, medical investigations in this area are inadequate and there is no conclusive evidence-based information. Pregnant cases are excluded from clinical trials, and most of the current safety data for psoriasis treatment is obtained from case reports. However, it is very important to maintain a balance between the risk of uncontrolled psoriasis and the risk of treatment in order not to develop maternal and fetal adverse results [8,9]. The recommendations for the use of antipsoriatic drugs during lactation are based on the limited data obtained by comparing maternal serum levels and infant serum levels at birth, and comparing breast milk levels and infant serum levels. Although there is no major concern about the use of topical agents in lactation, it is recommended to wipe the breast before breastfeeding due to the possibility of passive transfer with skin contact [9,10,17].

There are still some difficulties in treatment due to the lack of well-established guidelines in pregnant women with psoriasis. However, United States and European drug labeling now summarize safety data on pregnancy and lactation to inform treatment choice in this patient population [8,48]. According to the international consensus decision, moisturizers and low-medium potency corticosteroids are recommended as the first option in the treatment of psoriasis during pregnancy [7,49]. While the uses of topical high potency steroids and topical calcipotriol are not recommended in this period, these topical agents can be used especially from the 3rd trimester [50-54]. However, even though the topical absorption of vitamin D analogues (calcipotriol or calcipotriene) is low, there are some concerns about their use as there is no data on safety. Both topical and systemic use of retinoids with known teratogenic effects are not recommended in any period of pregnancy and lactation. Methotrexate is one of the well-known agents that should be avoided both during pregnancy and lactation due to its mutagenic, teratogenic and abortogenic properties. Psoralen + Ultraviolet A (PUVA) therapy should also not be preferred during both pregnancy and lactation due to mutagenic potential of psoralens [7,9,51-54]. However, it has been suggested that topical PUVA therapy for palmoplantar psoriasis may be relatively safer, especially from the 3rd trimester [9]. In these periods, the most appropriate treatment after topical agents is broadband or especially narrow band Ultraviolet B (UVB) phototherapy. In terms of possible maternal folate photodegradation of phototherapy and so the risk of fetal neural tube defects, women of childbearing age should receive adequate folic acid supplementation before conception and in the first trimester. The facial region should be protected as the risk of melasma increases during treatment. It is also known that the risk of preeclampsia is higher with long-term exposure to high temperatures in the summer, so UVB treatment is thought to be more reliable after the first trimester [55]. However, in patients who do not respond to UVB phototherapy, systemic steroids can be used especially in the presence of generalized pustular psoriasis of pregnancy. It should be remembered that when systemic steroids are used in the first trimester they may lead to cleft palate/lip, and may cause low birth weight and growth retardation in subsequent periods. In addition, a rebound effect may develop while treatment is discontinued, and sometimes there may be a transformation into atypical clinical forms such as erythrodermic or pustular psoriasis. When using systemic steroids during lactation period, breastfeeding the baby should be avoided up to 4 hours after drug intake due to its half-life. Another option that can be used in pregnancy in patients with resistant psoriasis is cyclosporine [7,51-54]. It is not teratogenic but has been associated with low birth weight and prematurity in transplant patients. Its use is not recommended during the lactation period as the transfer rate to breast milk varies [56].

The treatments that should be considered in the next stage in resistant patients with psoriasis are agents blocking TNF-α (etanercept, certolizumab, adalimumab, infliximab). Before these medications, patients should be evaluated especially for latent infections (e.g., tuberculosis), malignancies and demyelinating diseases. There are different recommendations in the literature regarding the use of anti-TNF-α agents in patients with psoriasis during pregnancy and lactation [57-63]. Although these agents have been reported as pregnancy category B, there are only a few reports of anomalies in VACTERL syndrome (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities) [64,65]. However, there is not yet enough data to reach a definitive conclusion, and it has been highlighted



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that these anomalies may be biased because they actually reflect negative outcomes collected by the FDA [66,67]. Data on the safety of anti-TNF-α treatments during pregnancy are increasing gradually [59-61]. Since these treatments are mostly used in inflammatory bowel diseases and rheumatoid arthritis, most of the data have been obtained from the literature of gastroenterology and rheumatology [68,69]. In a systematic meta-analysis of 13 studies conducted in patients with chronic inflammatory diseases, it has been found that pregnancy outcomes and neonatal complications in women exposed to anti-TNF-α agents during pregnancy have comparable results to women who did not receive anti-TNF-α [69]. In another recent meta-analysis evaluating 1300 pregnant women treated with anti-TNF-α, there is a tendency to indicate drug-specific side effects (such as an increase in congenital malformation and preterm delivery) but none are significant [70]. On the other hand, in a more recent population-based study, it was found that anti-TNF-α agents were associated with increased risks of preterm birth, caesarean section, and small for gestational age. However, the authors stated that the diverse findings across disease groups in this study may indicate an association related to the underlying disease activity rather than to agent-specific effects [71]. As a general approach, it is recommended that women using anti-TNF-α avoid pregnancy and be monitored if they have already become pregnant, but there is no conclusive evidence that adalimumab, infliximab, etanercept and certolizumab pegol treatments are embryotoxic or teratogenic [59-61]. Therefore, it has been reported that the continuation of the treatment according to the risk-benefit balance should be decided individually in each patient. The main concern is possible infections that may occur in newborns and infants associated with anti-TNF-α. It is known that biological agents with long half-life and monoclonal antibody structure pass through the placenta from the 16th week. Therefore, it is recommended to avoid the use of this group of treatments in the last trimester of pregnancy. Etanercept should be considered as the first choice due to its short half-life and being a fusion protein [53,67]. Placental transfer of biologics increases over time and peaks in the 3rd trimester, and it can be detected in the serum of infants up to six months after birth. For this reason, it is recommended that live vaccines (e.g., BCG, rotavirus vaccines) should not be administered to babies of mothers with psoriasis who use anti-TNF-α biological therapy during pregnancy for at least the first six months of life [57-59]. Exceptionally, the only agent that can overcome this rule is certolizumab, which does not have a placental transfer from mother to baby. Nevertheless, United States and European certolizumab labels indicate that the theoretical risk of administering live or live-attenuated vaccines to infants exposed to this biological agent inutero should be weighed against the benefits of these vaccines [8,63]. On the other hand, inactive vaccines that are routinely administered can be applied to babies whose mothers used anti-TNF-α agents during pregnancy [57-59]. The use of biological agents in lactation is considered to be moderately safe [49,51,58]. Due to greater safety data for anti-TNF-α agents, it should be considered before the monoclonal antibodies targeting IL-12/IL-23 or IL-17 cytokines in the treatment of pregnant women with psoriasis [57-60]. Further, large pharmacovigilance studies are needed for the safety of these new agents in pregnancy.

## Conclusion

Although the presence of psoriasis does not constitute a contraindication for pregnancy and there is no evidence that fertility is negatively affected, it is necessary to carefully manage the disease and closely monitor maternal comorbidities during preconception and pregnancy periods. In order to fully understand the effects of the presence, clinical type, severity and treatments of psoriasis, as well as the effects of accompanying maternal comorbidities on the pregnants and infants, performing large cohort studies with multivariate modelling is needed in the future.

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DOI: https://dx.doi.org/10.17352/aap.000013