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REVIEW ARTICLE

Pregnancy in patients with immune-mediated inflammatory diseases

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Abstract

A large percentage of patients with immune-mediated inflammatory diseases (IMIDs) are women of childbearing age. Pregnancy is a complex physiological scenario and causes significant endocrine and immunological changes. Pregnancy can trigger a worsening of IMIDs and, bidirectionally, disease flares are associated with worse pregnancy outcomes. This highlights the importance of achieving adequate control of IMIDs before conception and during pregnancy. When choosing pharmacological therapy in pregnant women with IMIDs, it is important to be aware of all available options and their potential impact on the mother and fetus. The aim of this review is to highlight the influence of pregnancy on the clinical evolution and prognosis of the most common cutaneous, rheumatological, and gastroenterological IMIDs. In addition, we provide an updated review of the different systemic and topical therapies used for the treatment of common dermatoses (such as atopic dermatitis, psoriasis, and hidradenitis suppurativa) and their safety profile during pregnancy and lactation.

Keywords: *Inflammatory disorders. Pregnancy. Breastfeeding. Therapy. Outcome.*

Introduction

Immune-mediated inflammatory diseases (IMIDs) are characterized by a female preponderance and usually debut during a woman's reproductive years. Thus, they are among the most common pre-existing diseases in pregnancy. The course of the disease can be highly variable during pregnancy, ranging from symptom improvement to exacerbations of the disease, leading to maternal and fetal complications. Associated obstetric complications often include variably increased rates of miscarriage, intrauterine fetal death, fetal growth retardation, and preterm delivery.

Given that women with IMIDs have potentially high-risk pregnancies, it is important to seek the most effective and safe drug profile possible during this period to optimize outcomes. When choosing drug therapy in pregnant women with IMIDs, it is important to be aware of all available options and their potential impact on the mother and fetus.

However, the use of systemic immunosuppressive drugs in pregnant women can be challenging. Some of the systemic drugs prescribed in the treatment of IMIDs are potentially teratogenic, while, for others, there is insufficient experience of use in human pregnancies and their potential impact on fertility, pregnancy, fetal, and neonatal development is not fully understood. The evidence is mainly based on observational studies and is often limited.

The aim of this review is to highlight the impact of pregnancy on the clinical evolution and prognosis of the most common cutaneous, rheumatological, and gastroenterological IMIDs. Although these diseases share several therapeutic options, in this review, we will focus on the safety profile during pregnancy and lactation of the different systemic and topical therapies used for the treatment of atopic dermatitis (AD), psoriasis, and hidradenitis suppurativa (HS).

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Cutaneous IMIDs

Atopic dermatitis

AD is the most common skin disorder during pregnancy and usually debuts during the second or third trimester. During gestation, the immune system is biased toward a T helper 2 (Th2)-dominated immune response, with the goal of inducing tolerance in the fetus. Because AD itself is a Th2-driven disease, women with AD are at increased risk of experiencing disease flares during pregnancy[1].

The previous studies have shown that about 25% of women with AD improve during pregnancy, while more than 50% have a worsening of disease symptoms, with worsening occurring most frequently in the second or third trimester of pregnancy (Table 1)[2,3].

Contrary to the tendency of AD to worsen during pregnancy, a study involving 10,441 pregnancies of women with AD revealed a pattern of increased use of topical corticosteroids (TCS) and ultraviolet (UV) light treatment, concomitant with decreased use of topical calcineurin inhibitors (TCI), and systemic treatments, compared to pre-pregnancy use. This may reflect a tendency for women to endure more DA flares during pregnancy, combined with a more cautious, and restricted treatment approach[1].

However, under-treated AD could negatively affect maternal well-being and fetal development, so careful risk-benefit assessment and choice of appropriate treatment during pregnancy are necessary. The social isolation effect of AD and its physiological impact on fertility has not been fully investigated. Some data from the literature suggest that the systemic inflammation found in patients with asthma may affect the uterine mucous layer (decidua) and thus impair effective implantation of the embryo[4]. For other atopic diseases, such as AD, this relationship with reduced fertility is less clear[4].

Similarly, studies focusing on potential pregnancy complications directly related to AD are scarce. Neonatal staphylococcal septicemia, eczema herpeticum, and premature rupture of membranes are currently the only reported complications that are significantly increased in pregnant patients with AD[1]. To date, no evidence of increased rates of infertility, prematurity, low birth weight, miscarriage, stillbirth, or congenital malformations has been found in this population (Table 1)[2,3].

Therapeutic guideline recommendations for atopic dermatitis in pregnant patients

Topical treatment

Emollients, TCS, and TCI are the first-line treatments for pregnant women with AD and are considered safe treatments before conception and during pregnancy and lactation (Fig. 1)[5].

The treatment with potent or very potent TCS has been associated with an increased risk of low birth weight when the total dose exceeds 300 g throughout pregnancy[6,7]. There is no increased risk of preterm birth or malformations associated with TCS use during gestation[6,7].

Fetal exposure depends on the steroid used: non-fluorinated steroids (prednisolone and methylprednisolone) are metabolized in the placenta by the enzyme 11-beta-hydroxysteroid dehydrogenase, whereas fluorinated steroids (betamethasone and dexamethasone) are metabolized at a much slower rate. In addition, fluticasone propionate is the only TCS that should not be used during pregnancy, as it crosses the placental barrier without being metabolized and can, therefore, reach the fetus in high concentrations[6,7].

However, if the amount of TCS used exceeds 200 g/month, treatment may reach systemic exposure levels, which indicates poorly controlled disease and is considered a risk factor. In this case, as an alternative to increasing the dose, a second drug to complement the main drug, or a therapeutic escalation to phototherapy should be considered[5].

Furthermore, due to the side effect of TCS in decreasing dermal elasticity and thus increasing the risk of stretch marks development, alternative topical treatments, such as TCI, may be considered in susceptible areas (face, intertriginous areas, or thighs).

On the other hand, there are no studies on the use of TCI during pregnancy; however, oral tacrolimus has been widely used in pregnant women after solid organ transplantation, with no observed teratogenic or mutagenic effects[8]. Although an increased risk of prematurity has been demonstrated, it may be associated with baseline maternal disease[8]. In addition, systemic absorption of TCI, due to the large size of the molecules, is negligible and no tendency for their accumulation has been found.

Phototherapy

Narrowband UVB (NB-UVB) and UVA1 phototherapy are considered second-line treatment in pregnant patients with AD who do not respond to topical treatments[5].

Table 1. Summary of available information regarding IMIDs clinical course during pregnancy and influence on maternal/fetal outcome

Inflammatory disorders	Disease course during pregnancy	Pregnancy outcome*
Atopic dermatitis	Worsening likely	Generally uneventful
Psoriasis	Improvement likely	Generally uneventful
Hidradenitis suppurativa	Worsening likely but controversial findings	Poor outcome likely
Rheumatoid arthritis	48-60% improvement, 40% stabile or worse	Poor outcome likely
Systemic lupus erythematosus	Worsening likely, especially if active disease or < 6 months' remission	Poor outcome likely, especially if active disease or < 6 months' remission
Inflammatory bowel disease	A third of patients develop flare activity	Poor outcome likely, especially if active disease or < 6 months' remission

*The table illustrates the information in brief, please consult the text for details. IMIDs: immune-mediated inflammatory diseases.

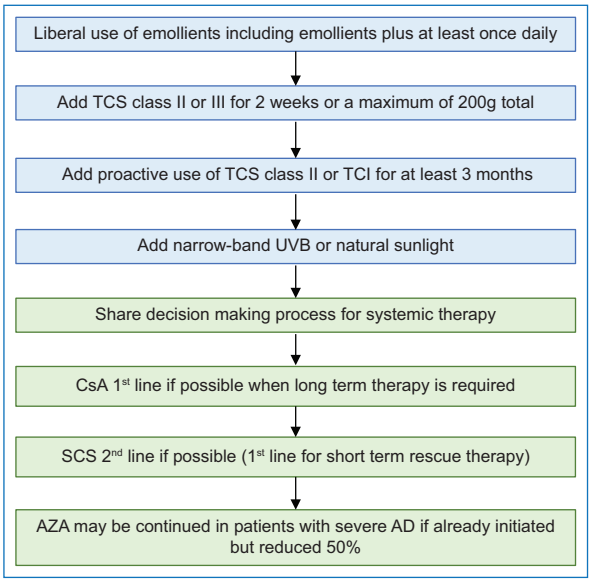

Figure 1. Algorithm for the treatment of pregnant women with atopic dermatitis[5].

UVB radiation is not considered teratogenic and can be used during pregnancy. However, pregnant women are at increased risk of developing melasma after UV exposure[5]. There is also evidence that UVB therapy can decrease serum folic acid levels, and this should be monitored at least once per trimester and compensated with folic acid supplementation (0.5-0.8 mg/day) before conception and during pregnancy[5]. In contrast, psoralen is not recommended preconceptionally (3 months) or during pregnancy due to its potential mutagenic effect[5].

Classical systemic therapy

Classical systemic therapy is the next therapeutic step if the disease cannot be controlled with topical treatment and UV therapy (Fig. 1).

Systemic corticosteroids

Systemic corticosteroids (SCSs) are occasionally used in non-pregnant AD patients as short-term treatment in acute and severe flares. Long-term use is not recommended due to serious side effects, including osteopenia, osteoporosis, type 2 diabetes, high blood pressure, glaucoma, infections, adrenal suppression, stretch mark formation, acne, and others[5]. During pregnancy, SCS may also increase the risk of gestational diabetes, pre-eclampsia, and even premature rupture of membranes and preterm delivery[5]. Studies of SCS use during pregnancy have not shown increased risk of teratogenicity, but repeated courses of treatment may result in decreased birth weight and increased incidence of gastrointestinal reflux in neonates[9]. The previous studies have suggested an increased risk of cleft palate in newborns when the mother was treated with SCS during pregnancy; however, this association was not confirmed in a later Danish cohort study involving 1449 women who used inhaled or oral corticosteroids before conception or during the first trimester of pregnancy[10].

Although the current literature shows that there appears to be no evidence of prolonged neonatal adrenal suppression in mothers treated with SCS during pregnancy, some studies recommend that infants born to mothers treated with > 35 mg/day of prednisolone should maintain an observation period of 48 h[11]. On the other hand, SCS treatment during lactation is safe, as < 0.1% of the dose ingested by the mother is excreted in breast milk[5].

SCS treatment appears to be safe in pregnant women provided that the mother and newborn are adequately monitored. The latest guidelines of the European Task Force on Atopic Dermatitis (ETFAD) recommend that the use of systemic glucocorticoids in patients with AD should be restricted to short-term treatment (< 2-3 weeks),

only if TCS and UV therapy has failed, and that the daily dose should not exceed 0.5 mg/kg/day[5].

If SCS treatment is needed in pregnant patients with AD, prednisolone, not dexamethasone, should be used[5].

Cyclosporin A

There is abundant evidence on the safety of cyclosporin A (CsA) use in pregnancy from studies focusing on patients with solid organ transplantation or systemic autoimmune diseases.

CsA crosses the placenta and the fetal serum concentration is up to 64% of the maternal concentration. A slightly increased risk of preterm birth and low birth weight has been demonstrated in newborns of mothers exposed to the drug during gestation; however, this could be attributed to the patients' underlying diseases. No teratogenic or mutagenic effects or fetal death associated with its use have been observed[5]. CsA is excreted in breast milk and can be transmitted to the fetus[5]. However, most publications indicate that breastfeeding is safe and that the amount ingested by the infant has no adverse effects, although monitoring of serum CsA concentrations in the newborn is currently recommended[5].

However, possible impairment of renal function or the development of high blood pressure is common side effects, and therefore, these parameters should be closely monitored during pregnancy. Based on these data, CsA can be used during the preconception period, pregnancy, and lactation in special cases, when the maternal benefit justifies the potential risk to the fetus. ETFAD classifies CsA as first-line systemic treatment during pregnancy when long-term systemic therapy is required for adequate disease control[5].

Azathioprine

Azathioprine (AZA) is most commonly used to treat inflammatory bowel disease (IBD) and other autoimmune diseases (such as systemic lupus erythematosus), but, in many countries, it is used off-label as an immunosuppressant to treat AD and is considered a treatment option for pregnant women with severe AD[5].

Evidence for AZA use during pregnancy comes from studies in patients with IBD. No teratogenic or mutagenic effects on the fetus have been observed, but it does seem to be associated with an increased risk of preterm delivery[12]. Maternal intake does not lead to immunosuppression in infants, and the rate of infection and hospitalization is not increased in children exposed to AZA *in utero* or through breastfeeding when followed up at 3 years of age[13].

Therefore, AZA can be used off-label for patients with AD before conception, during pregnancy and lactation, in isolated cases, when topical therapy, UV, and CsA treatment have failed, are not tolerated or are contraindicated for any reason[5]. Close monitoring by an experienced obstetrician is strongly recommended when prescribing this drug during pregnancy.

Methotrexate

Methotrexate (MTX) is used off-label for the treatment of severe AD in non-pregnant patients when other systemic drugs have been ineffective. MTX does not decrease the chances of conception[14]. However, the drug is teratogenic and contraindicated during pregnancy.

Because MTX blocks DNA synthesis, the drug is associated with severe birth defects, including craniofacial anomalies, limb defects, cardiovascular defects, genital defects, and mental retardation when administered during pregnancy[14]. Even low-dose exposure (< 20 mg/week) can cause birth defects[14]. Therefore, in cases of inadvertent exposure during pregnancy, termination of pregnancy is not warranted, but the treatment should be stopped immediately and ultrasound should be offered to examine fetal development[14].

In breastfeeding, MTX is excreted in breast milk, but at concentrations of < 10% of maternal serum concentrations. Since even these low doses have been found to cause immunosuppression and neutropenia in infants, MTX treatment during lactation is discouraged[14]. The European League Against Rheumatism (EULAR) working group recommends discontinuing MTX 1-3 months before conception in planned pregnancies[15], while the European Medicines Agency (EMA) establishes a recommended drug washout period of up to 6 months before conception.

Mycophenolate mofetil (MMF)

MMF prevents DNA synthesis by inhibiting purine synthesis through blockade of the enzyme inositol monophosphate dehydrogenase. MMF is teratogenic and is associated with a high rate of spontaneous abortions and a cluster of specific embryonic malformations known as MMF embryopathy, including microtia, aural atresia, cleft lip and palate, hypertelorism and polydactyly, as well as abnormalities in the central nervous system (CNS), renal, and cardiovascular systems[16]. There are no data on the consequences of MMF use in lactating women; however, it is secreted into milk, so breastfeeding is not recommended during MMF treatment. There are currently no studies on its impact on fertility[16].

MMF is absolutely contraindicated in patients with AD during preconception, pregnancy, and lactation and also in male patients with AD with reproductive desire, until at least 3 months before conception[5].

Biological therapy

Information on the use of biologics for the treatment of atopic disorders during pregnancy is limited in humans[4]. This causes great uncertainty in clinical decision-making when adequately treated women with good therapeutic response to biologics plan to conceive or become pregnant. The treatment is often discontinued due to lack of safety data.

At present, the body of evidence is restricted to small observational studies and case reports, and information on the safety of biologics in pregnancy comes mainly from extrapolation of studies in patients with IBD and rheumatological diseases. Although atopic diseases are among the most common diseases of reproductive age, there is a lack of research and information on the pharmacokinetics and, more importantly, on the safety of these treatments.

Dupilumab

Dupilumab is a fully humanized IgG4 monoclonal antibody directed against the alpha subunit of the interleukin (IL)-4 receptor, blocking both the IL-4 and IL-13 signaling pathways. It is currently approved for the treatment of severe AD, severe asthma, and chronic rhinosinusitis with nasal polyposis.

There are no studies to date on fertility, pregnancy complications, embryotoxicity, or breastfeeding consequences. Animal studies have not indicated direct or indirect harmful effects on fertility or adverse effects on their offspring[17]. To date, only two case reports of patients who maintained dupilumab during pregnancy have been published: one patient who maintained dupilumab throughout pregnancy and lactation; and the other patient who started dupilumab treatment at 24 weeks gestation due to an AD flare with poor response to other treatments. In both cases, no fetal or maternal complications were reported[18,19]. However, the current experience is anecdotal.

Human IgG antibodies are known to cross the placental barrier; therefore, this drug may be transmitted from the mother to the developing fetus. IgG levels in the fetal circulation increase after week 13, reaching 50% at weeks 28 to 32, and may exceed maternal levels after week 35[4]. In addition, among the different types of immunoglobulins, IgG4, in particular, is transported across the placental barrier at a high rate (IgG1 > IgG4 > IgG3 > IgG2). Due to the immature reticuloendothelial system, it has been proposed that there is reduced clearance of biologics in infants[4].

In general, contraception should be maintained during therapy. Due to the paucity of safety data available on the potential complications of dupilumab treatment during pregnancy and the consequences of exposure to the fetus, dupilumab is currently not recommended before conception or during pregnancy or lactation[4].

Tralokinumab

Tralokinumab is a new anti-IL-13 antibody recently approved by the Food and Drug Administration (FDA) and EMA for the treatment of severe AD in 2021.

There are no published data on its use in pregnant women, nor has the necessary washout period before conception been specified[20]. Prenatal and postnatal studies with tralokinumab in monkeys have not identified adverse effects on mothers or their offspring up to 6 months postpartum. However, because its effects in humans are unknown, it is recommended that tralokinumab use during pregnancy be avoided as a precautionary measure[20].

JAK inhibitors

A number of novel therapies are now available for the treatment of AD. Baricitinib is the first Janus kinase (JAK) inhibitor that has been approved by the FDA and EMA for the treatment of severe AD in adult patients[21]. It is a small molecule that inhibits both JAK1 and JAK2[21].

Very limited data are available on the safety of JAK inhibitors in pregnancy and on female fertility. Reproductive toxicology studies have shown no adverse fetal effects in animals exposed to baricitinib at twice the approved human concentration. However, at concentrations approximately 10-39 times the human label dose, a reduction in fertility and a teratogenic effect, with decreased fetal growth and weight and skeletal malformations have been observed, respectively, in rats and rabbits[21]. There are no data on the impact of its use during lactation and it is unknown whether it can be transferred to human milk[21].

Based on these findings, baricitinib is contraindicated in pregnancy and during lactation, and women of childbearing age are advised to use effective contraception during and at least 1 month after treatment[22]. To date, one case has been reported of maternal exposure to baricitinib during pregnancy, preconceptionally, and

during the first trimester up to 17 weeks of gestation, in a patient with rheumatoid arthritis (RA), resulting in a healthy full-term infant[21].

The other JAK inhibitors recently approved by the FDA and EMA for the treatment of severe AD, upadacitinib, and abrocitinib, are also contraindicated during pregnancy. Both drugs are elective oral JAK1 inhibitors and were developed with the aim of improving the safety profile by minimizing the effects of blockade on JAK3 and JAK2[23].

Although there are no data on their effects in pregnant women, embryofetal development studies in animals have shown them to be teratogenic in rats and rabbits. At human doses (15 and 30 mg), upadacitinib caused increased skeletal malformations and increased rate of post-implantation abortions in rats and cardiovascular malformations in rabbits[23]. Regarding abrocitinib, to date, no data on its effects on fertility, fetal development, pregnancy, and lactation have been reported. Therefore, the data for both products recommend that women of childbearing age use effective contraception during treatment and for 4 weeks after the final dose of upadacitinib and abrocitinib.

Psoriasis

Psoriasis is a chronic IMID that affects 1-3% of the world's population[24]. The prevalence is similar in men and women, and the disease usually debuts before the age of 40[24]. Therefore, in routine clinical practice, a large percentage of patients with psoriasis managed by dermatologists are women of childbearing age[24].

The course of psoriasis may fluctuate throughout pregnancy as hormone levels change. The current literature points to a trend toward an improvement in the clinical course of the disease during pregnancy, with a slight risk of exacerbations after delivery. It has been reported that approximately 55% of patients have an improvement of the disease during pregnancy, 21% remain stable, and 23% of women experience an exacerbation of psoriasis (Table 1)[24].

After delivery, the proportion changes: approximately 9% of patients show improvement; 26% remain stable; and 65% experience a worsening of their disease, with most returning to their pre-pregnancy baseline level of activity[24]. In addition, psoriasis is associated with other problems, such as the potential impact of anti-psoriatic treatments and the disease itself on fertility or the possible involvement of localized disease in the nipple and breast area, making breastfeeding difficult[24].

Regarding fetal impact, psoriasis, particularly uncontrolled disease, has been associated with adverse outcomes such as low birth weight neonates, preterm delivery, pre-eclampsia, small-for-gestational-age fetuses, and fetal loss[24]. However, this association between psoriasis and adverse pregnancy events remains unclear at present and is the subject of recent publications. The study by Tsao *et al.*[25] shows that underlying conditions are important features to consider as potential confounders for pregnancy outcomes. Gestational risk factors such as obesity, dyslipidemia, depression, diabetes, and hypertension should be excluded, and the fact that these comorbidities are often associated with psoriasis may be a confounding bias in adverse pregnancy outcomes. Therefore, it is likely that the negative impact on fetal development is due to maternal baseline comorbidities or drug exposure, rather than direct and potentially harmful psoriasis-related inflammation (Table 1)[25].

Therapeutic guideline recommendations for psoriasis in pregnant patients

During pregnancy, the treatment with low-to-moderate potency topical steroids is recommended as first line and narrowband ultraviolet B phototherapy as second line therapy in limited disease (Fig. 2)[26]. It is advised that psoriasis be controlled or in remission before conception to minimize possible flares during pregnancy[27,28].

However, in patients with severe disease, there may be a strong need to continue or introduce systemic therapy. Among the available classical systemic treatments, methotrexate, acitretin, and other systemic retinoids are teratogenic and contraindicated during pregnancy (FDA category X). It is also recommended to discontinue treatments with systemic PUVA (psoralen and ultraviolet A), apremilast, and dimethyl fumarate due to their potential teratogenic effects. Therefore, only cyclosporine and systemic steroids (in the second and third trimester) can be used in pregnant patients after appropriate risk-benefit counseling (FDA category C)[27,28]. Specific treatment with biologics, despite having revolutionized the natural history of the disease, is not generally recommended during the preconception period, pregnancy, and lactation due to the lack of clinical safety trials.

Detailed information on the potential impact on pregnancy of classical systemic psoriasis drugs is discussed in the AD and HS treatment sections.

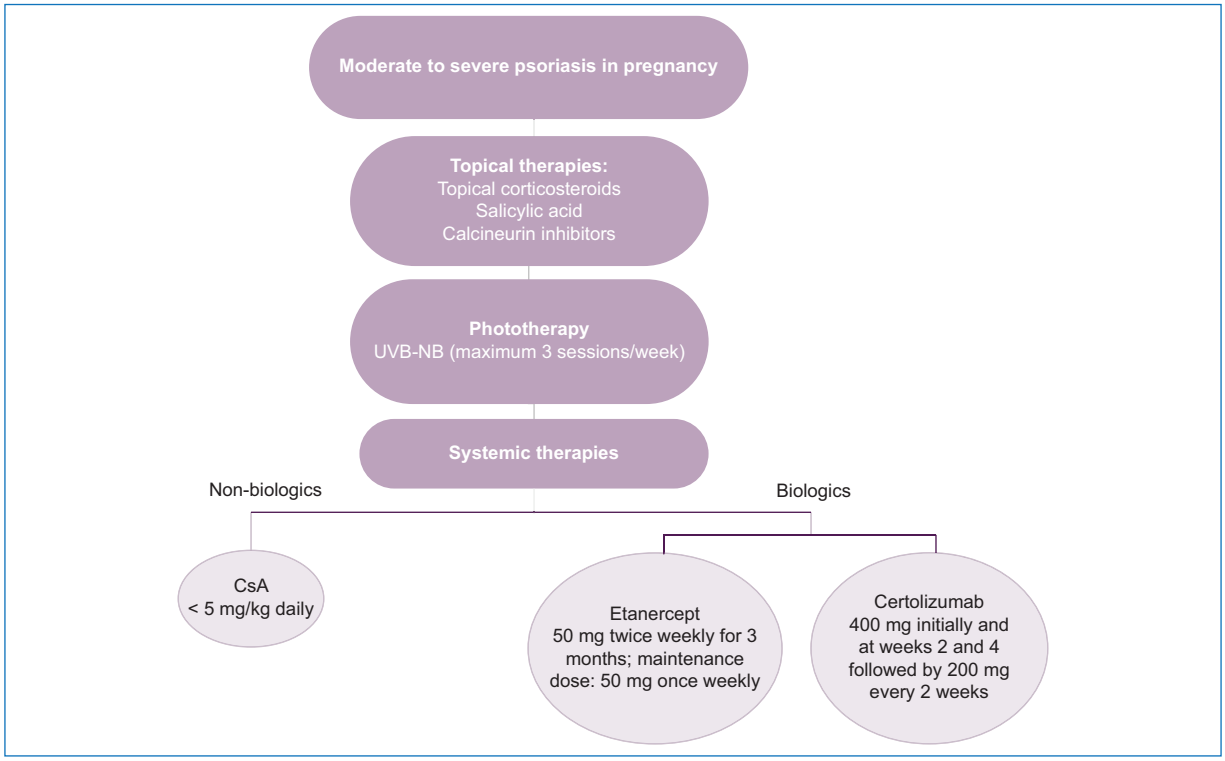

Figure 2. Algorithm for the treatment of pregnant women with psoriasis *(modified from Timis et al. 2021)*[26].

Biologic therapy

Biologics currently approved by the FDA and the EMA for the treatment of moderate-to-severe psoriasis are classified into the following groups: tumor necrosis factor (TNF)-α inhibitors (infliximab, adalimumab, etanercept, and certolizumab pegol), interleukin (IL)12 and IL23 p40 monoclonal antibodies (ustekinumab), anti-IL17A antibodies (secukinumab, ixekizumab, and brodalumab), and IL23 p19 subunit inhibitors (guselkumab, risankizumab, and tildrakizumab).

Most of these drugs are IgG monoclonal antibodies and are actively transported across the placenta through the Fc receptors of the syncytiotrophoblast and cannot cross the placenta by simple diffusion due to their size (> 100 kDa). It is thought that, due to the absence of Fc receptors in the first trimester, there is no fetal exposure to biologic drugs during early embryogenesis and the risk of teratogenicity is low[27,28].

As exceptions, etanercept (fusion protein) has lower affinity for placental Fc receptors, and reduced or no placental transfer has been reported for certolizumab pegol (pegylated human IgG1 monoclonal antibody), as it lacks an Fc receptor[27,28]. Given its molecular structure, certolizumab pegol is considered the most appropriate anti-TNF for use during pregnancy and lactation.

At present, decision-making about continuing or initiating biologic therapy in pregnant patients remains complex due to limited knowledge about the long-term safety of intrauterine exposure. PSOLAR[29], a multicenter observational registry evaluating pregnancy outcomes of women with psoriasis who received biologic therapy during gestation or the prenatal period, reported that rates of miscarriage, neonatal problems, and congenital malformations were similar to those of the general US population.

However, there are conflicting results in the literature. Three systematic reviews[30-32] from 2018, 2019, and 2021 reported that pregnant women with chronic inflammatory diseases (including psoriasis) exposed to anti-TNFα therapy had an increased risk of congenital malformations, small-for-gestational-age fetuses, neonatal infections, and preterm pregnancies. A subsequent meta-analysis[25], which included studies with adjusted odds ratios, did not show an increase in congenital malformations associated with biologic use in pregnant women with chronic inflammatory diseases, suggesting that adverse effects may

be due to disease activity or other confounding factors.

Another important aspect to consider is the possibility of an altered immune response in newborns of patients who continue treatment with biologic agents during the past months of pregnancy and, in particular, until the third trimester[27,28]. The Centers for Disease Control and Prevention (CDC) recommends, given the rate of placental transmission of antibodies during the second and third trimester of gestation, postponing the administration of attenuated vaccines during the first 6 months of life to newborns born to mothers who continue treatment with monoclonal antibodies after 20 weeks of gestation, because an increased risk of infections due to neonatal immunosuppression and even fatal cases, such as a disseminated BCG (Bacillus Calmette-Guerin) infection in a newborn whose mother had been treated with infliximab for Crohn's disease, has been reported[33]. Inactivated vaccines can be administered according to CDC-recommended guidelines.

Current guidelines from Psoriasis Group of the Spanish Academy of Dermatology and Venereology, EMA, and British Association of Dermatologists 2020 recommend preconception counseling and advocate the use of contraception in women of childbearing age receiving biologic therapy as long as pregnancy is not contemplated or when it is preferable to postpone pregnancy. It is advisable to interrupt, if possible, biologic treatment in the second and third trimester to minimize exposure and fetal risk[27,34]. If clinically necessary, the use of anti-TNFα is preferred, with certolizumab pegol as first line, and discontinuation of other biologics[27,34]. Among anti-TNFα drugs, for structural reasons, etanercept and certolizumab pegol can be administered until later in pregnancy: Etanercept until 30-32 weeks of gestation and throughout pregnancy for certolizumab pegol. However, continuation of treatment should be discussed individually with patients, considering all risks and benefits.

Recommendations for the use of anti-TNF therapy in the treatment of patients with rheumatologic diseases suggest continuing therapy safely until 30 weeks of pregnancy[35]. The most recent consensus statements from the Canadian Gastroenterological Association state that women at low risk of IBD relapse should stop anti-TNF therapy at 22-24 weeks, but, in all other cases, it is recommended that women with IBD receiving anti-TNF therapy continue treatment throughout pregnancy[36].

At present, infliximab, etanercept, adalimumab, certolizumab pegol, ustekinumab, and secukinumab are classified in FDA pregnancy category B, while no FDA category is assigned to newer biologics[27,28,37].

Hidradenitis suppurativa

HS is a chronic inflammatory dermatosis characterized by painful nodules and sinus tracts draining purulent material, typically located in the intertriginous areas. A population-based study in the United States found that the average annual incidence of HS was 12.1/100,000 women, more than double that of men (5.1/100,000)[38]. Furthermore, people aged 30-39 years had the highest incidence, followed by those aged 18-29 years, corresponding to women's childbearing years[38].

Hormones are thought to play a role in the pathogenesis of HS[38]. It has been suggested that increased progesterone levels during pregnancy may play a protective role in at least a subset of HS patients by promoting the differentiation of immunomodulatory Th2 and regulatory T-cells, while suppressing the release of pro-inflammatory Th1/Th17 cytokines. However, although about a quarter of women with HS may experience an improvement in their disease during pregnancy, the majority women with HS have a stable or worsening disease course[39]. In addition, more than half of women (60%) experience a postpartum disease flare (Table 1)[40].

In addition, childbirth also poses a challenge for patients with HS. A 2020 study found that up to 3.1% of patients with anogenital HS who delivered vaginally, HS interfered with delivery[41]. Of the patients who reported having a cesarean delivery, 33.9% reported poor incision healing and 51.2% reported the development of new inflammatory nodules over the cesarean scar[41].

Women with HS also have significantly lower odds (52%) of having a live birth compared to women without HS (70.74%)[42]. In addition, women with HS have been reported to be 2.51 times more likely to have an elective termination of pregnancy, as well as a higher risk of gestational hypertension and cesarean delivery, compared to healthy women[42]. Similarly, in a retrospective cohort study, pregnancies with HS were independently associated, after adjusting for maternal comorbidities, with increased risk of miscarriage, gestational diabetes mellitus, and cesarean section, compared to control pregnancies (Table 1)[43].

Regarding lactation, having HS lesions in the breasts can be a real obstacle. In fact, there are a limited number of options for pharmacological treatment of HS during lactation[38]. Deciding between treatment options for women with worsening HS during pregnancy or lactation requires an understanding of the efficacy and safety profile of drugs for both mother and fetus. In this document, we provide a review of the safety of commonly used drugs for HS. General recommendations are summarized in table 2.

Topical antiseptic washes: chlorhexidine and benzoyl peroxide

Topical antiseptic washes with antimicrobial activity may help reduce immune activation to resident skin bacteria in HS patients[44]. Chlorhexidine is considered FDA pregnancy category B; human data are lacking; however, animal studies have failed to demonstrate fetal harm and it is currently considered safe during pregnancy. On the other hand, topical application of chlorhexidine to the breast has not been shown to adversely affect infants[44].

Benzoyl peroxide wash is minimally absorbed through the skin and, if absorbed, is metabolized to benzoic acid, which is naturally found in certain foods. It is, therefore, considered safe during pregnancy[44].

Topical antibiotics: clindamycin, erythromycin, and metronidazole

Topical antibiotics may be considered for use in mild disease (Hurley Stage I and II). Topical clindamycin, erythromycin, and metronidazole are considered FDA pregnancy category B. When applied topically, they have very low systemic absorption, so the possibility of harm to the fetus is remote. These topicals are also considered compatible with breastfeeding, although further safety studies are needed[44].

Systemic antibiotics: clindamycin, metronidazole, rifampicin, moxifloxacin, and dapsone

Combination therapy with oral clindamycin (B) and rifampicin (C) is indicated for any stage of active disease and is considered first-line treatment in moderate-severe disease outside of pregnancy[44].

Systemic administration of clindamycin during the second and third trimester has not been associated with an increased frequency of congenital malformations. However, since there are no adequate studies during the first trimester, this agent should only be used if clearly needed. Clindamycin is excreted in small concentrations within breast milk and its use during lactation may have the potential to affect the infant's gastrointestinal flora, but it has generally been considered safe during breastfeeding by the American Academy of Pediatrics (AAPs)[44].

Rifampicin has been shown in rodent studies to be teratogenic at oral doses 15-25 times higher than the human dose[44]. In humans, a review including observational studies with more than 2000 exposures during pregnancy did not observe an excessive rate of congenital malformations[44]. However, rifampicin has been shown to cause postnatal hemorrhage in the mother and infant when administered during the past weeks of pregnancy. Prophylactic administration of vitamin K1 is, therefore, recommended to prevent this complication[44]. Rifampicin should only be considered if the potential benefits outweigh the risks to the mother and fetus. Although rifampicin is excreted into human breast milk, it is not known to cause adverse effects to nursing infants and is considered compatible during lactation[44].

The combination of rifampicin (C)-moxifloxacin (C)-metronidazole (B) has also demonstrated efficacy in the treatment of II and III Hurley stage recalcitrant HS[44].Although human data suggest a low risk of moxifloxacin use during pregnancy, studies have concluded that fluoroquinolones should be avoided due to possible fetal cartilage damage, as safer alternatives are generally available[44]. According to studies in rats, moxifloxacin may also be excreted in breast milk increasing the risk of arthropathy, although no human data are available. It is best to use caution and avoid moxifloxacin during pregnancy and lactation when possible[44].

Metronidazole has been shown to cross the placenta and rapidly enter the fetal circulation. However, overall, human data suggest a low risk of fetal harm[44]. Metronidazole is also secreted into breast milk at concentrations similar to plasma concentrations[44]. The AAP recommends discontinuing the medication 12-24 h before breastfeeding[45].

Dapsone (C) is a third-line agent for the treatment of Hurley Stage I or II disease[44]. There are no warnings of fetal abnormalities with use in any trimester; however, it can cause neonatal hyperbilirubinemia and dose-related hemolysis in the mother and infant[44]. Hemolysis may be important in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency, so initial measurement of G6PD levels should be performed. Dapsone is excreted in breast milk and dapsone-induced hemolytic

Table 2. Summary of guidance regarding medication use for hidradenitis suppurativa during pregnancy and breastfeeding[44]

Guidance	Pregnancy (FDA pregnancy category)	Breastfeeding (FDA pregnancy category)
Generally considered safe	Topical therapies: – Chlorhexidine (B) – Benzoyl peroxide – Clindamycin (B) – Erythromycin (B) – Metronidazole (B) Systemic therapies: – Clindamycin (B) – Metronidazole (B) – Metformin (B) – Zinc	Topical therapies: – Chlorhexidine (B) – Benzoyl peroxide – Clindamycin (B) – Erythromycin (B) – Metronidazole (B) Systemic therapies: – Clindamycin (B) – Rifampin (C) – Adalimumab (B) – Infliximab (B) – Metformin (B) – Zinc
Caution advised	Systemic therapies: – Rifampin (C) – Moxifloxacin (C) – Dapsone (C) – Adalimumab (B) – Infliximab (B) – Colchicine (C) – Apremilast (C) – Cyclosporine (C) – Corticosteroids (C)	Systemic therapies: – Metronidazole (discontinue 12-24 h before breastfeeding) (B) – Moxifloxacin (C) – Dapsone (C) – Colchicine (C) – Apremilast (C) – Corticosteroids (C) – Spironolactone (C)
Avoid	Systemic therapies: – Tetracyclines (D) – Acitretin (X) – Isotretinoin (X) – Finasteride (X) – Spironolactone (C) – Methotrexate (X)	Systemic therapies: – Cyclosporine (C) – Tetracyclines (D) – Acitretin (X) – Isotretinoin (X) – Finasteride (X) – Methotrexate (X)

FDA: Food and Drug Administration.

anemia has been reported in infants[45]. Caution is, therefore, advised with the use of dapsone during pregnancy and lactation.

Non-biologic immunomodulators: colchicine and apremilast

Colchicine (C) is known to cross the placenta. Animal studies have shown teratogenicity at concentrations within or above the therapeutic range. However, in a prospective observational cohort study of 238 colchicine-exposed pregnancies, it did not appear to be a major human teratogen or to have cytogenetic effects[46]. It is also excreted in breast milk, although limited data suggest that breastfed infants receive less than 10% of maternal dose[44]. However, colchicine may affect infant gastrointestinal system by influencing cell turnover and permeability[44]. Given these data, colchicine should be used with caution during pregnancy and breastfeeding[47].

Apremilast (C) has demonstrated efficacy in the treatment of patients with mild-to-moderate HS[44]. The incidence of teratogenicity and fetal loss in humans has not been established. However, exposure during organogenesis in monkeys revealed an increase in embryofetal death at doses 2.1 times the maximum recommended human therapeutic dose. Apremilast has been detected in lactating mice, but it is not known whether apremilast or its metabolites are present in human breast milk. Given the lack of data on the safety during pregnancy and lactation, caution should be exercised and this agent should only be used if the benefits clearly outweigh the risks[44].

Immunosuppressants: systemic corticosteroids and cyclosporine A

The potential effects caused by the use of SCS and CsA during pregnancy have been previously discussed in AD treatment section.

Biologic therapy: adalimumab, infliximab, ustekinumab, certolizumab pegol, secukinumab, and anakinra

Among anti-TNF-α agents, adalimumab, certolizumab, and infliximab have shown efficacy in the treatment of moderate-to-severe HS. On the other hand, ustekinumab and secukinumab and anakinra (IL-1 antagonist) have also been used in the treatment of HS with good results.

Recommendations for the use of anti-TNF-α drugs, ustekinumab, and secukinumab during pregnancy and lactation have been discussed previously (*see psoriasis*). Regarding the use of anakinra, although current evidence remains insufficient to establish recommendations for its use in pregnancy, a review of 40 pregnancies exposed to anakinra found no increase in the rate of miscarriage or congenital malformations in newborns[15].

Adjunct therapies: metformin and oral zinc

During pregnancy, metformin (B) can be considered as adjuvant therapy as it has not been shown to cause fetal adverse effects[44]. In general, metformin is considered compatible with breastfeeding, although there is a potential risk of hypoglycemia in infants[44].

Zinc supplementation has also demonstrated clinical efficacy in a small cohort of HS patients. Safety data during pregnancy are lacking; however, review studies investigating the use of up to 50 mg daily revealed no maternal or neonatal adverse effects[44].

Other treatments

Tetracyclines (D) have traditionally been used for the treatment of mild disease (I or II Hurley stage). This class of antibiotics has been associated with acute fatty liver of pregnancy when exposed in the third trimester. First trimester exposure has not shown an increased risk of congenital anomalies. Therefore, tetracycline use is contraindicated during late pregnancy[44]. Short-term use of tetracyclines may be considered during lactation; however, administration should be discontinued before 3 weeks of use to prevent dental staining. More research is needed on the use of tetracyclines during pregnancy and lactation, but they should generally be avoided[44].

Spironolactone (C) is beneficial as adjuvant or monotherapy in the treatment of HS. However, it leads to feminization of male fetuses and should be avoided during pregnancy. There is no evidence of adverse effects for infants with short-term exposure, but long-term data are lacking, so avoidance of use during lactation is currently recommended[44].

Other drugs used in the treatment of patients with HS, but totally contraindicated during pregnancy and lactation (category X) include: oral retinoids (acitetrine and isotretinoin), finasteride, and MTX.

Rheumatological IMIDs

Rheumatoid arthritis

The prevalence of RA in women of childbearing age is around 0.2%[48]. Pregnant women with RA have an approximately 1.5-2 times higher risk of hypertensive complications, fetal growth restriction, preterm delivery, and cesarean delivery. Venous thromboembolism occurs 2 to 4 times more frequently than in healthy pregnant women. Preterm delivery and growth restriction have been associated with disease activity and high-dose SCS treatment[48].

RA activity tends to be favorably affected by pregnancy. Improvement in disease activity has been reported in 48-60% of women with RA during pregnancy (Table 1). After delivery, 39-50% of women may experience a flare of the disease. Furthermore, conception should be planned at a time when the disease is fully controlled or its activity is minimal and, if possible, maintenance therapy compatible with both pregnancy and breastfeeding should be continued, especially due to the high risk of flares after delivery[48].

Systemic lupus erythematosus

The initial manifestation of systemic lupus erythematosus (SLE) occurs predominantly before the age of 30 years. The prevalence is estimated at 55/100,000 in the female population. The incidence of fetal, maternal, and obstetric complications is significant, including increased risk of preterm birth, growth restriction, pre-eclampsia, and thromboembolic disease, with disease activity being one of the most important risk factors[48]. The increased risk of preterm birth and pre-eclampsia arises from a combination of high clinical and serological activity, increasing in the case of positive antiphospholipid antibodies and lupus nephritis[48].

The likelihood of outbreaks is increased by 60% in pregnant patients compared to non-pregnant patients (Table 1). This risk depends on disease activity before conception, so pregnancy should be planned after

6-12 months of absence or mild disease activity. During the pre-conception phase, treatment should be reviewed and continued or switched to acceptable and safe immunosuppressive therapy during pregnancy to maintain remission. Hydroxychloroquine should always be initiated or continued if not contraindicated. Low-dose acetylsalicylic acid (ASA) is recommended for the prevention of pre-eclampsia in all patients[48].

Antiphospholipid syndrome develops in the setting of SLE in approximately 20% of cases. Antiphospholipid antibodies are associated with an increased risk of thrombosis and obstetric complications, especially late miscarriage and placental insufficiency. Depending on clinical and serological parameters, the treatment consists of ASA and/or heparin[48].

Gastroenterological IMIDs

Inflammatory bowel diseases

The prevalence of IBD, Crohn's disease, and ulcerative colitis is 300 and 400/100,000, respectively, with a peak incidence in the third/fourth decade of life[48].

Disease activity at the time of conception has the greatest effect on the course of the disease during pregnancy. Therefore, the current guidelines advise that conception should be planned during a remission period of at least 6 months[49]. Under these ideal conditions, about one-third of patients experience a flare during pregnancy (Table 1). On the other hand, active IBD at the time of conception is associated with preterm delivery, growth restriction, and an increased rate of the early miscarriage[50].

Clinical signs of increased disease activity are difficult to differentiate from symptoms that often develop during pregnancy, such as abdominal pain, nausea, rectal bleeding from hemorrhoids, and symptoms of anal stricture/constipation. Fecal calprotectin, unlike hemoglobin, C-reactive protein, and albumin, is not altered by pregnancy and, as such, appears to be adequate for predicting impending flares[48]. Gastrointestinal ultrasonography correlates well with fecal calprotectin and has a reliable negative predictive value; however, after 20 weeks of gestation, it is often not possible to adequately visualize the terminal ileum[48].

Patients with perianal involvement should receive proctological treatment in addition to primary, internal medical/gastroenterological, and obstetric/prenatal care. Regarding delivery, the European guidelines advise avoiding episiotomy, due to the risk of fistula formation[49]. Crohn's disease with perianal fistulas or proctitis is indications for elective cesarean section[49].

Conclusions

Close collaboration between dermatologists, rheumatologists, gastroenterologists, and obstetricians is needed to ensure adequate follow-up of pregnant patients with IMIDs. Large prospective registries of pregnant women may improve our understanding of the impact of IMIDs on pregnancy.

Finally, evidence-based consensus guidelines are urgently needed to assist in the appropriate management of these patients. The literature on the treatment of IMIDs during pregnancy and lactation is scarce, especially with regard to new biologics and small molecule therapies. Since interventional studies are not possible in this patient group, we emphasize the importance for specialists to publish any available cases.

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Conflicts of interest

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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