ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Type 2 inflammatory diseases: safety profile of biologics and small molecules during pregnancy

Doenças inflamatórias do tipo 2: perfil de segurança de imunobiológicos e pequenas moléculas na gestação

Catarina Monteiro Palumbo[1], Marcelo Vivolo Aun[1,2]

ABSTRACT

Type 2 chronic inflammatory diseases are highly prevalent among women of childbearing age. When poorly controlled, they are associated with pregnancy complications, which justifies the study of different options for their management. This study aimed to review the literature on the use of advanced therapies, such as biologics and small molecules, for type 2 diseases, focusing on their safety profile during pregnancy. Observational studies available in the literature from 2010 to 2024 were analyzed to determine the risk of maternal and fetal complications arising from exposure to these medications during pregnancy. No randomized clinical trials involving human participants were found on the topic. No study showed a direct association between exposure to omalizumab or dupilumab and negative outcomes. There is insufficient evidence in humans to predict increased risk of complications with the use of mepolizumab, benralizumab, tezepelumab, reslizumab, or tralokinumab. Janus kinase inhibitors are absolutely contraindicated after conception due to risks observed in animal studies. Further research is needed to better understand the safety of advanced therapies during pregnancy, with the goal of making more informed clinical decisions in the future.

Keywords: Molecular targeted therapy, pregnancy, asthma, atopic dermatitis, hypersensitivity.

RESUMO

As doenças inflamatórias crônicas do tipo 2 são altamente prevalentes em mulheres em idade fértil. Quando mal controladas, se associam a complicações gestacionais, o que justifica o estudo de diferentes alternativas para o seu manejo. Esse artigo objetiva revisar a literatura sobre o uso de terapias avançadas, como imunobiológicos e pequenas moléculas, em doenças do tipo 2, com enfoque em seu perfil de segurança durante a gestação. Foram analisados os estudos observacionais disponíveis na literatura de 2010 a 2024, visando avaliar o risco de complicações maternas e fetais advindas da exposição a estas medicações na gestação. Não foram encontrados ensaios clínicos randomizados em humanos sobre o tema. Em nenhum estudo sobre omalizumabe e dupilumabe a exposição foi diretamente associada a desfechos negativos. Não há dados suficientes em humanos para predizer aumento de risco de complicações no uso de mepolizumabe, benralizumabe, tezepelumabe, reslizumabe ou tralokinumabe. Os inibidores das Janus quinase são absolutamente contraindicados após a concepção, pelo risco observado na exposição de animais. São necessários mais estudos sobre o tema, para melhor compreensão da segurança de terapias avançadas na gestação, visando decisões clínicas mais embasadas no futuro.

Descritores: Terapia de alvo molecular, gravidez, asma, dermatite atópica, hipersensibilidade.

Introduction

Chronic type 2 inflammatory diseases, such as atopic dermatitis (AD), asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and eosinophilic esophagitis (EoE), are a group of conditions with varied phenotypes but shared pathophysiological characteristics, which taken together affect 20–30% of

1. Hospital Israelita Albert Einstein, Faculdade Israelita de Ciências da Saúde Albert Einstein - São Paulo, SP, Brazil.
2. Faculdade de Medicina da Universidade de São Paulo, Disciplina de Imunologia Clínica e Alergia - São Paulo, SP, Brazil.

Submitted Sep 17 2024, accepted Oct 10 2024.
Arq Asma Alerg Imunol. 2024;8(4):377-90.

http://dx.doi.org/10.5935/2526-5393.20240051-en

the world population.[1,2] Chronic spontaneous urticaria (CSU), despite having a distinct pathophysiology, is associated with atopy and also involves the main cells and molecules of type 2 inflammation, sharing some of its therapeutic targets.[3,4]

Poor control of these conditions is associated with morbidity and reduced quality of life, with high direct and indirect societal costs.[5] Although there are well-established and individualized management strategies, many patients do not tolerate conventional therapies or do not achieve complete remission of symptoms with these therapies alone. The advent of advanced therapies, such as biologics and advanced small-molecule drugs, has revolutionized the treatment and prognosis of these conditions, allowing more effective control of disease activity.[6]

The prevalence of allergic diseases in women of childbearing age is estimated at 18–30%.[7] During pregnancy, a series of immune-system changes result in dominance of the T helper 2 (Th2) cell response throughout the fetal growth period, which may predispose women with these diseases to flares, worsening of symptoms, or even onset of new atopic conditions.[8] Some of the first-line drugs of choice for management are also contraindicated in pregnancy, and must be discontinued after conception. However, inadequate disease control is consistently associated with adverse maternal and fetal outcomes.[9-12]

Currently, of the 11 medicinal products approved by the U.S. Food and Drug Administration (FDA) for the management of type 2 inflammatory diseases,[6] none are formally indicated for use during pregnancy. There are no randomized clinical trials demonstrating safety in this population[13]; however, there are multiple records of pregnant patients who received biologicals and small molecules for these indications between 2010 and 2024. The aim of this study is to conduct a comprehensive review of the literature on the use of advanced therapies for asthma, chronic rhinosinusitis with nasal polyps, atopic dermatitis, eosinophilic esophagitis, and chronic spontaneous urticaria, with a focus on their safety profile during pregnancy.

Background

Pathophysiology of type 2 inflammation

The type 2 immune response is classically defined as an adaptive response which involves the activation of Th2 lymphocytes and the release of group 2 effector cytokines, culminating in the recruitment of eosinophils and the production of IgE.[14,15] This pattern of immune response can be triggered by helminths, but also by other pathogens and irritating substances.[16,17] Allergens can trigger a non-targeted, dysregulated Th2 inflammatory response, resulting in allergies, anaphylaxis, and atopic diseases.[14,17] The host skin and epithelial barrier play an important protective role against noxious environmental stimuli and invasion by parasites.[17] In patients with persistent inflammation, the epithelial barrier is damaged, exacerbating and perpetuating atopic diseases.[18]

Exposure to exogenous insults triggers the release by epithelial cells of alarmins, such as thymic stromal lymphopoietin (TSLP), interleukin (IL) 25, and IL33. These substances play a role in the activation of antigen presenting cells (APCs)[19] and ILC2 cells—major sources of IL5 and IL13[15]—even before the onset of the adaptive immune response.[14] APCs present antigens in lymph nodes,[19] leading to activation of naive CD4 T lymphocytes into Th2 lymphocytes and the production of effector cytokines such as IL4, IL5, and IL13.[14] The process of polarization toward the Th2 response has not been completely elucidated, but appears to be mediated by the presence of alarmins.[14,20]

Th2 lymphocytes interact with B lymphocytes (BLs),[21] resulting in the production of IgE by an IL4- and IL13-dependent mechanism.[6] IL4, in addition to encouraging the differentiation of more immature T lymphocytes into Th2, induces isotype switching in BLs. IL13, in turn, mediates the proliferation of IgE-producing BLs.[19] IL5 stimulates the development of eosinophils, promoting activation of their precursors in the bone marrow, maturation, and differentiation.[6,22] In the bloodstream, eosinophils release cytotoxic protein granules that induce tissue damage and dysfunction.[22] They also play roles in the regulation of mast cell proliferation and degranulation.[6,22]

IgE antibodies activate mast cells and basophils, releasing histamine, leukotrienes, tryptase, and prostaglandins, which perpetuate the inflammatory response through the recruitment of immune cells[6] and act on the epithelial barrier, resulting in hypersecretion of mucus and contraction of smooth muscle cells.[16]

Several signaling pathways are involved in type 2 inflammation. Highlights among these include the Janus kinase (JAK) and Bruton's tyrosine kinase (BTK) pathways, which have been studied as targets for the development of advanced therapies.[6] Suppression of the type 2 immune response is carried out by regulatory T (Treg) and B (Breg) lymphocytes,

which secrete IL10 and transforming growth factor beta (TGF-β). The activity and concentration of these regulatory factors appears to be altered in type 2 inflammatory diseases.[6,23]

Type 2 inflammatory diseases in pregnancy

The prevalence of allergic diseases in woman of childbearing age ranges from 18 to 30%, with asthma, AD, allergic rhinitis, and food allergies being most common.[7] During pregnancy, several immune adaptations occur, aiming to strike a balance between effective immunity against pathogens and appropriate immunomodulation for each stage of fetal development. While more pro-inflammatory states are required for implantation, placentation, and during the third trimester, an anti-inflammatory immune milieu predominates throughout the fetal growth stage.[8]

Between 13 and 27 weeks of gestation, the period of fetal and placental growth, the immune response shifts to a dominance of the Th2 pattern and a key role for regulatory lymphocytes. Treg and Th9 lymphocytes control effector lymphocyte responses against paternal antigens, protecting fetal cells from rejection and apoptosis, which helps promote an anti-inflammatory environment.[8,24] Type 2 cytokines are also believed to be involved in maternal-fetal tolerance.[24] However, exacerbation of Th2 immunity during this period may be associated with onset or clinical deterioration of autoimmune and/or atopic diseases.[13,24]

Asthma is the most prevalent respiratory disease in this group, affecting up to 13% of pregnant women worldwide. Although the course is variable, approximately 30% of women experience a worsening of symptoms during pregnancy. Asthma exacerbations have a negative impact on maternal and fetal outcomes and may be related to reduced prescription and adherence to medications during the gestational period. Guidelines generally recommend continuing any drugs used before conception, but this is hindered by a lack of evidence on their safety profile.[25]

Multiple studies have demonstrated a significant association between poorly controlled asthma and negative maternal and fetal outcomes. In a systematic review and meta-analysis by Wang et al.[9] based on 40 prospective and retrospective cohorts, maternal asthma was significantly correlated with increased risk of gestational diabetes, cesarean section, antepartum hemorrhage, postpartum hemorrhage, placental abruption, and premature rupture of membranes. An update of the systematic review and meta-analysis by Robijn et al.[10] on neonatal adverse events in pregnant women with asthma demonstrated a high risk of congenital malformations, perinatal mortality, and neonatal hospitalization. However, compared to the original study,[26] the risk of neonatal death lost statistical significance.

AD is the most common dermatosis during pregnancy, accounting for 30–50% of cutaneous conditions in this population.[27] In 80% of cases there is no previous history of AD, while the remaining 20% are recurrences or relapses occurring after conception.[28] Among women with eczema, the course of the disease varies during pregnancy; approximately half experience worsening of symptoms, especially in the second trimester.[27] This can be explained by the immune-system changes discussed above, but also by the consequences of hormonal changes in the skin. Recent studies indicate that estrogen has a positive impact on the epithelial barrier, while progesterone appears to have a negative effect. These hormones also stimulate Th2 lymphocytes and alter the cytokine balance, contributing to gestational atopic eruptions.[29]

Preconception planning should include measures to reduce disease activity to a minimum,[27] as few systemic therapies for AD have been proven safe during pregnancy. Emollients and low-to-medium-potency topical corticosteroids are considered first-line treatments. UVA1 and UVB therapies are restricted to more serious cases, as is ciclosporin, which is a pregnancy category C drug. Other topical and systemic medications may be considered; however, the evidence base is limited.[29]

Maternal and fetal outcomes of pregnancies in patients with eczema are poorly studied. In a Danish retrospective cohort, Hamann et al.[11] found statistical significance of AD as a protective factor against gestational diabetes mellitus and as a risk factor for premature rupture of membranes and staphylococcal neonatal sepsis. These associations, however, were not sustained in an analysis adjusted for BMI. Another possible complication, although few cases have been reported, is eczema herpeticum during pregnancy. Eczema herpeticum develops secondary to compromised epithelial integrity[30] and may be associated with miscarriage, premature birth, and intrauterine growth restriction.[27]

There are few data in the literature on CRSwNP during pregnancy. It is estimated that around 18–30% of pregnant women experience symptoms of

rhinitis, which significantly worsen their quality of life, especially in the third trimester.[31] There are no studies on the prevalence of CRSwNP in this population. Maternal and fetal outcomes have also been scarcely studied.

Management of CRSwNP during the gestational period is based on corticosteroids, with topical agents being preferable to systemic ones.[32] Alhussien et al.[33] concluded that fluticasone propionate, mometasone, and budesonide are the safest options during pregnancy. There are no data in the literature regarding the maintenance or introduction of biologics in pregnant women with this condition.

CSU affects 3–5% of the population at some point in their lives, occurring most frequently in women.[34] Despite the severity of this condition in female patients, there is little data regarding their follow-up during pregnancy. The PREG-CU study by Kocatürk et al.[35] evaluated 288 women with this disease in 13 countries. Of these, 63% discontinued or changed treatment after conception. Antihistamines were the most commonly used medications, and were not associated with worse maternal or fetal outcomes. There were no differences in complications between women with CSU and the general population. Urticaria flares requiring emergency treatment were significantly associated with preterm birth, suggesting that robust disease control is essential during pregnancy.[35]

Although more frequent in males, EoE still has a substantial prevalence in women (32.83 cases per 100,000), with incidence peaking between the second and third decades of life.[36,37] Huang et al.[37] did not report adverse gestational events related to the use of systemic corticosteroids during pregnancy. A cohort study by Röjler et al.[36] did not demonstrate any positive association between presence of EoE and low birth weight, instrumental delivery, induction of labor, gestational diabetes, or preeclampsia. However, there is still little information on its proper management and possible complications during pregnancy.

Advanced therapies

Advanced therapies have revolutionized the treatment and prognosis of atopic diseases, allowing more effective control of disease activity and, in many patients, remission of symptoms. Currently, there are 7 biologics approved by the U.S. FDA for use in these conditions: omalizumab, dupilumab, mepolizumab, benralizumab, tezepelumab, reslizumab, and tralokinumab. In addition, there are four small-molecule targeted therapies: abrocitinib, upadacitinib, baricitinib, and ruxolitinib. Table 1 summarizes key information on these advanced therapies.[6,38-56]

In Brazil, the following have been approved by Anvisa (the National Health Regulatory Authority) for the treatment of asthma: omalizumab, dupilumab, mepolizumab, tezepelumab, and benralizumab.[49-53,57] An international consensus published in 2024[58] including 141 experts involved in asthma treatment in 32 countries concluded that biologics can be used during preconception, pregnancy, and breastfeeding in women with severe asthma. Among them, omalizumab, mepolizumab, benralizumab, reslizumab, and dupilumab achieved consensus (≥ 75% of respondents). There was also agreement that these therapies can be started during pregnancy, with the same indication criteria applied to non-pregnant women and an emphasis on shared decision-making with the patient.

Advanced therapies approved for AD management in Brazil are dupilumab, abrocitinib, upadacitinib, and baricitinib.[50,54-56] For CRSwNP, the therapeutic armamentarium includes omalizumab, dupilumab, and mepolizumab.[49-51,59] Both the FDA and Anvisa have approved dupilumab for EoE[39,50] and omalizumab for CSU.[38,49]

Other medications are in clinical development and/or at different phases of clinical research. Potential therapeutic targets of interest include cytokines (TLSP, IL33, and ST2), IL4/ IL4 Rα and IL13/ IL13 Rα1, IL5 and IL-5Rα, JAK, IgE, BTK, mast cells, and various others (IL31, IL-31Rα, NK1R, CCR4, GATA3, OX40, OX40L).[6]

Safety profile of advanced therapies during pregnancy

The use of advanced therapies during pregnancy is poorly supported by evidence, and there is no formal indication for their prescription during this period.[38-48] Table 2 summarizes the pregnancy risk categories assigned to each of these medications. Pregnancy category B refers to medications in which animal studies have not been associated with increased fetal risk, but controlled studies have not been conducted in pregnant women. This category also includes drugs in which animal studies have demonstrated risks which were not confirmed by subsequent controlled studies in humans. Category C includes medications in which animal studies have demonstrated risk to the fetus,

Table 1
Advanced therapies currently approved by the FDA and Anvisa

Drug (trade name)	Mechanism/ target	Indications (FDA and Anvisa approved) FDA	Anvisa	Route of administration
Omalizumab (Xolair®)	IgE	Asthma, CRSwNP, CSU	Asthma, CRSwNP, CSU	Subcutaneous
Dupilumab (Dupixent®)	IL4/13-Rα	Asthma, AD, CRSwNP, PN, EoE	Asthma, AD, CRSwNP, PN, EoE	Subcutaneous
Mepolizumab (Nucala®)	IL 5	Asthma, CRSwNP, EGPA, HES	Asthma, CRSwNP, EGPA, HES	Subcutaneous
Benralizumab (Fasenra®)	IL 5-Rα	Asthma	Asthma	Subcutaneous
Tezepelumab (Tezspire®)	TSLP	Asthma	Asthma	Subcutaneous
Reslizumab (Cinqair®)	IL 5	Asthma	N/A	Intravenous
Tralokinumab (Adbry®)	IL 13	AD	N/A	Subcutaneous
Abrocitinib (Cibinqo®)	JAK1	AD	AD	Oral
Upadacitinib (Rinvoq®)	JAK1	AD, RA, PA, UC	AD, RA, PA, UC, AS	Oral
Baricitinib (Olumiant®)	JAK1/2	AD, RA	AD, RA, AA	Oral
Ruxolitinib (Opzelura®)	JAK1/2	AD	N/A	Topical

FDA = Food and Drug Administration, ANVISA = Brazilian National Health Regulatory Agency, AD = atopic dermatitis, PN = prurigo nodularis, CRSwNP = chronic rhinosinusitis with nasal polyps, EoE = eosinophilic esophagitis, CSU = chronic spontaneous urticaria, RA = rheumatoid arthritis, UC = ulcerative colitis, PA = psoriatic arthritis, EGPA = eosinophilic granulomatosis with polyangiitis, HES = idiopathic hypereosinophilic syndrome, N/A = not approved, AS = ankylosing spondylitis, AA = alopecia areata.
Adapted from[6,38-56].

but controlled studies have not been conducted in humans.[60]

Because advanced therapies have specific biological targets, they are believed to carry a lower risk of adverse maternal and fetal outcomes when compared to conventional systemic drugs. However, there is evidence of transplacental passage of monoclonal antibodies, especially at the later stages of pregnancy, which could pose risks to the fetus.[13] The following section will review the available literature on use of these therapies during pregnancy.

Omalizumab

The use of omalizumab during pregnancy has been studied in patients with asthma and CSU. There are no randomized clinical trials. The EXPECT observational study, by Namazy et al.,[61] is a prospective cohort published in 2015 which analyzed 191 patients exposed to one or more doses of omalizumab at any time during pregnancy or up to 8 weeks before conception. Among the 169 pregnancies with reported outcomes, there were 160 live births (including 4 twin pregnancies), 1 stillbirth, and 11 miscarriages.

Table 2
Pregnancy risk categories of advanced therapies with marketing authorization in Brazil

Drug	Pregnancy risk category
Omalizumab	B
Dupilumab	B
Mepolizumab	B
Benralizumab	B
Tezepelumab	B
Abrocitinib	C
Upadacitinib	C
Baricitinib	C

Adapted from [49-56].

A total of 21 congenital anomalies were described, with a 4.4% rate of major defects and an 8.8% rate of conditional defects. Premature birth weight, low birth weight, and small for gestational age status were seen, respectively, in 14.5%, 3.2%, and 10.9% of cases. These findings did not differ from studies of fetal complications in patients with asthma not on biologics.

The QECC (Quebec External Comparator Cohort) study, published in 2020 by Namazy et al.,[62] compared the EXPECT cohort (n = 230) to a population of pregnant patients with asthma not on biologics (n = 1143). The prevalence of major birth defects was similar between groups (8.9% in QECC vs. 8.1% in EXPECT), which corroborates the conclusion that exposure to omalizumab does not appear to increase the risk of this outcome. Furthermore, the proportion of live births was similar in both studies (99.3% in QECC vs. 99.1% in EXPECT), with a higher number of small-for-gestational-age children in the former (15.8% in QECC vs. 9.7% in EXPECT).[61-62]

Another retrospective observational study, by Gemicioglu et al.,[63] analyzed 20 patients with asthma who had received at least one dose of omalizumab during pregnancy. There were 8 episodes of asthma exacerbation (36.4%), 5 cases of premature birth (21.5%), and 3 cases of low birth weight (13%). No congenital anomalies or other maternal-fetal outcomes were reported.

A retrospective analysis of the safety profile of omalizumab in women with CSU by Patruno et al.[64] found 1 miscarriage among 29 patients who received one or more doses during pregnancy or up to 8 weeks preconception. No other adverse events were observed, leading to the conclusion that the use of omalizumab for CSU does not appear to be associated with negative outcomes. A subgroup of EXPECT containing 30 patients with CSU was also analyzed by Namazi et al.[65] The results were similar to those found in asthma, and the study concluded that no increased risk was observed in the omalizumab group.

Finally, we reviewed 9 case reports, the main data and outcomes of which are compiled in Tables 3 and 4. Five patients with severe, difficult-to-control asthma and multiple exacerbations became pregnant while taking omalizumab and chose to continue it throughout pregnancy.[66-69] Three continued taking the drug until full term, while one discontinued use after the first trimester. Four episodes of exacerbation were reported. One patient[68] delivered a low-birth-weight female infant (544 g) prematurely in the 26th week of gestation. This may have been related to the severity

Table 3
Case reports on the use of omalizumab during pregnancy in patients with asthma[49-56]

Author	Timing of exposure	Patients	Exacerbations	Fetal complications	Maternal/ gestational complications	Live births
Majou et al.[66]	Throughout pregnancy	1	2	0	0	1
Kuprys-Lipinska et al.[67]	Throughout pregnancy	2	0	0	0	2
Hirashima et al.[68]	First trimester	1	1	Prematurity, low birth weight	0	1
Kuschnir et al.[69]	Throughout pregnancy	1	1	0	0	1

Table 4
Case reports on the use of omalizumab during pregnancy in patients with chronic spontaneous urticaria

Author	Timing of exposure	Patients	Exacerbations	Fetal complications	Maternal/ gestational complications	Live births
Liao et al.[70]	Variable	2	1	0	0	2
Losappio et al.[71]	Throughout pregnancy	1	0	0	0	1
González-Medina et al.[72]	Variable	2	0	0	0	2
Ghazanfar et al.[73]	Throughout pregnancy	1 (2 pregnancies)	0	0	1 post-term pregnancy (42 weeks)	2
Cuervo-Pardo et al.[74]	Throughout pregnancy	4	0	0	0	4

of her asthma prior to pregnancy. No congenital anomalies or other adverse maternal or fetal outcomes were observed.

The 10 patients with CSU who were monitored received omalizumab in the first trimester or throughout their pregnancies.[70-74] In one case, the drug was started after conception,[72] while in another, the dosage was increased at 12 weeks due to a severe exacerbation.[70] No stillbirths, miscarriages, premature birth weight, low birth weight, congenital birth defects, or other negative outcomes were reported.

There are no studies on the safety profile of this medication during pregnancy in women with CRSwNP. Omalizumab is currently classified as pregnancy category B by the FDA, but it is not approved for use during pregnancy.[38]

Dupilumab

The use of dupilumab during pregnancy was studied in women with AD and pemphigoid gestationis. An observational study on the use of systemic and topical therapies in the United States[75] estimated that, of 3,563 patients with the disease, 2% were taking this drug before conception. The data show that the drug was discontinued in most cases, with only 0.7% taking it in the first and 0.3% taking it in the second and third trimesters. This may be related to the lack of robust evidence proving the safety of this biologic during pregnancy.

An Italian retrospective cohort study by Avallone et al.[76] evaluated 29 patients with severe AD who received dupilumab during pregnancy. The drug was discontinued in all cases once pregnancy was discovered, with a median exposure time of 6 [2-24] weeks. There was no statistically significant difference in any gestational, fetal, or neonatal outcomes, even after multivariate analysis adjusted for confounders. Another observational study analyzed a worldwide pharmacovigilance database (VigiBase).[77] No perinatal adverse events were consistently associated with the use of dupilumab during pregnancy.

We have also reviewed 8 case reports[78-85] and 3 case series,[86-88] which are compiled in Table 5. The patients analyzed in these reports all started dupilumab for moderate to severe AD, with high Eczema Area Severity Index (EASI) scores, a large body surface area affected, significant impact on quality of life, and/or lack of disease control despite multiple previous trials of therapy. The most frequent comorbidities included asthma, rhinitis, and conjunctivitis. Improvement of symptoms and regression of AD were observed in all women.

In most cases, the drug was used throughout the gestational period. Only one case series[87] was restricted to preconception. All three patients in whom the drug was discontinued subsequently experienced disease flares,[78,80,84] with two requiring reintroduction of therapy. In one case[85] dupilumab was initiated during pregnancy (24 weeks).

Regarding maternal complications, there were two cases of gestational diabetes and one emergency cesarean section due to suspected intrauterine growth restriction.[80,84,85] Low birth weight was reported in a singleton pregnancy (2480 g) and in two premature twins born at 35 weeks (1500 g and 2000 g, respectively).[80,88] No congenital anomalies, miscarriages, stillbirths, or any other gestational or fetal adverse events were observed. Follow-up of offspring[78,86] showed no changes in growth or development. Dupilumab use by men during conception was not associated with any adverse outcomes.[87]

There are no randomized clinical trials on this topic. There are also no published articles on the use of dupilumab during pregnancy in patients with asthma who have comorbid CRSwNP or EoE.

Mepolizumab

There are no randomized clinical trials of mepolizumab during pregnancy. It has also not been studied in CRSwNP. We found only one case report, by Vittorakis et al.,[89] regarding treatment with biologics in a patient with severe eosinophilic asthma. During pregnancy planning, an attempt was made to discontinue mepolizumab, which resulted in a severe disease flare requiring reintroduction. The patient became pregnant and remained on medication throughout her gestation, experiencing only two disease flares which were treated with brief cycles of systemic corticosteroids. The child was born at 40 weeks of gestation, weighing 2750 g, with no birth defects. Maternal and fetal eosinophil counts after delivery were less than 1.5%. No gestational or neonatal adverse events were reported. Another report, by Ozden,[90] focused on two previously infertile patients who conceived after starting mepolizumab. One chose to terminate the pregnancy, while the other discontinued the medication and delivered a healthy infant with no congenital anomalies.

Table 5
Case reports and case series on the use of dupilumab for management of atopic dermatitis during pregnancy

Author	Timing of exposure	Patients	Exacerbations	Fetal complications	Maternal/ gestational complications	Live births
Di Lernia et al.[78]	Throughout pregnancy	1	1, after attempted withdrawal of medication	0	0	1
Alvarenga et al.[79]	Throughout pregnancy	1	0	0	0	1
Akhtar et al.[80]	Throughout pregnancy	1	1, after attempted discontinuation of dupilumab at 27 weeks (2480 g)	Low birth weight (2480 g)	Emergency cesarean section due to suspected intrauterine growth restriction	1
Costley et al.[81]	Throughout pregnancy	1	NRA	0	0	1
Gracia-Darder et al.[82]	Throughout pregnancy	1	0	0	0	1
Kage et al.[83]	Throughout pregnancy	1	0	0	0	1
Lobo et al.[84]	Up to 24 weeks of gestation	1	1, after discontinuation of dupilumab at 24 weeks	0	Gestational diabetes	1
Mian et al.[85]	Started after 24 weeks of gestation	1	NRA	0	Gestational diabetes	1
Hong et al.[86]	Variable 1-3 = 1st and 3rd trimesters 4 = 3rd trimester	4	1 mild 1 moderate 0 severe	0	0	4
Bosma et al.[87]	2 fathers at conception 2 mothers pre-conception	4	NRA	0	0	4
Escolà et al.[88]	Variable (average exposure 6.8 ± 2.9 months)	11	NRA	2 premature twins (35 weeks) with low birth weight (1500 g and 2000 g)	0	12 (1 twin pregnancy)

NRA = not reported in article.
Adapted from [78-88].

Benralizumab

We found a single case series by Naftel et al.[91] on the use of benralizumab for asthma during pregnancy. No adverse neonatal events, low birth weight, or congenital anomalies were observed in the four patients reported. All deliveries occurred at full term, except for one scheduled cesarean section at 36 weeks. One patient had a history of multiple asthma-related complications during previous pregnancies, including two premature births (at 32 and 36 weeks). After starting benralizumab, she achieved and maintained satisfactory control of her symptoms, with no complications during pregnancy. Flares were reported in two women, one of which was related to an attempt at drug discontinuation. The patient with the worst disease control was a smoker who did not cease her habit during pregnancy, and experienced four disease flares.

One case report by Saco and Tabatabaian[92] described significant worsening of asthma and eosinophilia after discontinuation of benralizumab in a pregnant patient. At 20 weeks of gestation, the decision was made to reintroduce the biologic, with significant improvement in the patient's condition. The report does not discuss any possible maternal or fetal complications. There have been no randomized clinical trials of benralizumab in pregnancy.

Tezepelumab

There are no published articles in the literature on the use of tezepelumab during human pregnancy. The FDA warns that any potential adverse events would be worse during the third trimester, as more substances cross the placental barrier during this period. A study of primates exposed throughout gestation to tezepelumab at doses more than 168 times that administered to humans demonstrated placental passage of the biologic, but no evidence of fetal adverse events.[42]

Reslizumab

There are no published studies on the use of reslizumab during human pregnancy. Studies in rodents exposed to 6 to 17 times the maximum recommended human dose did not find any fetal adverse events. However, this biologic is known to have a prolonged half-life and to cross the placental barrier, which may be associated with negative outcomes, particularly in the second and third trimesters.[43]

Tralokinumab

There are no published studies on the use of tralokinumab during human pregnancy. There is an ongoing study which is currently collecting data through an online platform.[93] In primates administered doses up to ten times higher than the maximum recommended human dose, no gestational or fetal developmental complications were reported.[44]

Small-molecule JAK inhibitors (abrocitinib, baricitinib, upadacitinib, ruxolitinib)

Expert consensus on systemic treatment of AD in special populations[94] contraindicates the use of all JAK inhibitors during pregnancy and lactation. This is based on the teratogenic effects reported for these drugs in animal studies. Accordingly, all patients of childbearing age on anti-JAK therapy are advised to use contraceptive methods.

There are no published articles in the literature on the use of abrocitinib during human pregnancy. A pregnancy outcomes registry is available but is still at the data collection stage. A safety analysis in rats exposed to 11 times the maximum recommended human dose demonstrated an increased incidence of skeletal variants and dystocia. An increase in fetal lethality and a reduction in postnatal survival were also observed at doses up to 17 times higher than recommended.[45]

Kammerer[95] reviewed cases of accidental exposure to baricitinib during pregnancy. Data extracted from a pharmacovigilance system found 77 maternal and 14 paternal exposures. Incidences of complications were similar to those recorded in the general population. The outcomes of interest included the number of live births, miscarriages, and elective terminations of pregnancy. Two fetal malformations were identified: anencephaly and hip dysplasia. In animal studies,[47] rodents exposed to 11 to 46 times the maximum recommended dose of baricitinib had a higher incidence of low weight and skeletal malformations. Increased fetal lethality has also been reported in rabbits. At 2- to 7-fold doses, no developmental changes were observed.

Rats exposed to 1.6 to 15 times the maximum recommended dose of upadacitinib had an increased incidence of skeletal malformations and low weight. In rabbits, an increased incidence of cardiac malformations, fetal losses after implantation, and low birth weight was observed.[46]

Finally, we found no studies on the use of topical ruxolitinib for AD during pregnancy. During drug development, oral administration of doses 22 times higher than recommended did not result in any congenital malformations in rodents.[48]

Final comments

Type 2 inflammatory diseases are highly prevalent in women of reproductive age, and their management during pregnancy is still controversial. Although not formally recommended after conception, some biologics are an acceptable second-line treatment option, especially for patients who cannot tolerate or are unable to achieve disease control with conventional therapies. Conversely, all small-molecule targeted therapies for these conditions are currently contraindicated during pregnancy and lactation.

The present article reviewed observational studies on the use of immunobiologics in humans during pregnancy. Among this class, omalizumab and dupilumab had the largest number of available studies, the findings of which do not demonstrate any increased risk of adverse outcomes directly related to treatment. Disease severity before conception is a major confounding factor in such studies, as poor control of type 2 inflammatory conditions is known to be associated with gestational complications. Furthermore, the sample sizes of exposed women are small, and all available studies are observational, which limits the validity of their conclusions.

There is a dearth of literature on mepolizumab and benralizumab, precluding any conclusions about their safety during pregnancy. There are also no published studies on the use of tezepelumab, reslizumab, or tralokinumab during human pregnancy. Animal studies have not found evidence of congenital malformations or any other complications. Again, the limited data precludes any conclusions regarding the potential gestational risk associated with these medications.

Conversely, animal studies with Janus kinase inhibitors have conclusively demonstrated fetal complications and malformations, which is consistent with the current absolute contraindication to their use during pregnancy.

Given the maternal and fetal risks, there have been no randomized clinical trials on this topic with any of the drugs of interest, which is a major limitation to generalization of our findings. The decision to continue therapy with biologics during pregnancy must be made on a case-by-case basis, considering the risk-benefit ratio for each patient. Further studies on this subject are needed to allow more evidence-informed clinical decisions in future.

References

1. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396:1204-22.
2. Bantz SK, Zhu Z, Zheng T. The Atopic March: Progression from Atopic Dermatitis to Allergic Rhinitis and Asthma. J Clin Cell Immunol 2014;5. https://doi.org/10.4172/2155-9899.1000202.
3. Chen Q, Wang W, Yang X, Li S, Deng S, Wang H, et al. Characteristics and Clinical Significance of Atopy in Chronic Spontaneous Urticaria: A Cross-Sectional Observational Study. Int Arch Allergy Immunol. 2024:1-6.
4. Maurer M, Kolkhir P, Pereira MP, Siebenhaar F, Witte-Händel E, Bergmann K-C, et al. Disease modification in chronic spontaneous urticaria. Allergy. 2024;79:2396-413. doi:10.1111/all.16243.
5. Zuberbier T, Lötvall J, Simoens S, Subramanian SV, Church MK. Economic burden of inadequate management of allergic diseases in the European Union: a GA(2) LEN review. Allergy. 2014;69:1275-9.
6. Kolkhir P, Akdis CA, Akdis M, Bachert C, Bieber T, Canonica GW, et al. Type 2 chronic inflammatory diseases: targets, therapies and unmet needs. Nat Rev Drug Discov. 2023;22:743-67.
7. Pfaller B, Bendien S, Ditisheim A, Eiwegger T. Management of allergic diseases in pregnancy. Allergy. 2022;77:798-811.
8. Mor G, Aldo P, Alvero AB. The unique immunological and microbial aspects of pregnancy. Nat Rev Immunol. 2017;17:469-82.
9. Wang G, Murphy VE, Namazy J, Powell H, Schatz M, Chambers C, et al. The risk of maternal and placental complications in pregnant women with asthma: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2014;27:934-42.
10. Robijn AL, Harvey SM, Jensen ME, Atkins S, Quek KJD, Wang G, et al. Adverse neonatal outcomes in pregnant women with asthma: An updated systematic review and meta-analysis. Int J Gynecol Obstet. 2024;166:596-606.
11. Hamann CR, Egeberg A, Wollenberg A, Gislason G, Skov L, Thyssen JP. Pregnancy complications, treatment characteristics and birth outcomes in women with atopic dermatitis in Denmark. J Eur Acad Dermatol Venereol. 2019;33:577-87.
12. Yawn B, Knudtson M. Treating asthma and comorbid allergic rhinitis in pregnancy. J Am Board Fam Med. 2007;20:289-98.
13. Ramos C, Namazy J. Monoclonal Antibodies (Biologics) for Allergic Rhinitis, Asthma, and Atopic Dermatitis During Pregnancy and Lactation. Immunol Allergy Clin North Am. 2023;43:187-97.
14. Lloyd CM, Snelgrove RJ. Type 2 immunity: Expanding our view. Sci. Immunol.3, eaat1604(2018). doi:10.1126/sciimmunol.aat1604.
15. McKenzie ANJ, Spits H, Eberl G. Innate lymphoid cells in inflammation and immunity. Immunity. 2014;41:366-74.
16. Pulendran B, Artis D. New paradigms in type 2 immunity. Science. 2012;337:431-5.
17. Palm NW, Rosenstein RK, Medzhitov R. Allergic host defences. Nature. 2012;484:465-72.

18. Schleimer RP, Berdnikovs S. Etiology of epithelial barrier dysfunction in patients with type 2 inflammatory diseases. J Allergy Clin Immunol. 2017;139:1752-61.
19. Akdis CA, Arkwright PD, Brüggen M-C, Busse W, Gadina M, Guttman-Yassky E, et al. Type 2 immunity in the skin and lungs. Allergy. 2020;75:1582-605.
20. Roan F, Obata-Ninomiya K, Ziegler SF. Epithelial cell-derived cytokines: more than just signaling the alarm. J Clin Invest. 2019;129:1441-51.
21. Abbas AK, Lichtman AH, Pillai S. Imunologia Celular e Molecular. 9th ed. Rio de Janeiro: Guanabara Koogan; 2019.
22. Rothenberg ME, Hogan SP. The eosinophil. Annu Rev Immunol. 2006;24:147-74.
23. Bellinghausen I, Khatri R, Saloga J. Current Strategies to Modulate Regulatory T Cell Activity in Allergic Inflammation. Front Immunol. 2022;13:912529.
24. Wang W, Sung N, Gilman-Sachs A, Kwak-Kim J. T Helper (Th) Cell Profiles in Pregnancy and Recurrent Pregnancy Losses: Th1/Th2/Th9/Th17/Th22/Tfh Cells. Front Immunol. 2020;11:2025.
25. Robijn AL, Murphy VE, Gibson PG. Recent developments in asthma in pregnancy. Curr Opin Pulm Med. 2019;25:11-7.
26. Murphy VE, Wang G, Namazy JA, Powell H, Gibson PG, Chambers C, et al. The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis. BJOG. 2013;120:812-22.
27. Weatherhead S, Robson SC, Reynolds NJ. Eczema in pregnancy. BMJ. 2007;335:152-4.
28. Munera-Campos M, Carrascosa JM. Atopic Dermatitis: Fertility, Pregnancy, and Treatment Perspectives. Am J Clin Dermatol. 2024;25:55-66.
29. Balakirski G, Novak N. Atopic dermatitis and pregnancy. J Allergy Clin Immunol. 2022;149:1185-94.
30. Gurvits GE, Nord JA. Eczema herpeticum in pregnancy. Dermatol Reports. 2011;3:e32.
31. Gilbey P, McGruthers L, Morency A-M, Shrim A. Rhinosinusitis-related quality of life during pregnancy. Am J Rhinol Allergy. 2012;26:283-6.
32. Carroll Jr. MP, Bulkhi AA, Lockey RF. Rhinitis and Sinusitis. In: Asthma, Allergic and Immunologic Diseases During Pregnancy. A Guide to Management. Springer Cham; 2019. p.61-86.
33. Alhussien AH, Alhedaithy RA, Alsaleh SA. Safety of intranasal corticosteroid sprays during pregnancy: an updated review. Eur Arch Otorhinolaryngol. 2018;275:325-33.
34. Robson M, Bernstein JS, Bernstein JA. Chronic Urticaria in Special Populations: Pediatric, Pregnancy, and the Elderly. Immunol Allergy Clin North Am. 2024;44:469-81.
35. Kocatürk E, Al-Ahmad M, Krause K, Gimenez-Arnau AM, Thomsen SF, Conlon N, et al. Treatment patterns and outcomes in patients with chronic urticaria during pregnancy: Results of PREG-CU, a UCARE study. J Eur Acad Dermatol Venereol. 2023;37:356-64.
36. Röjler L, Uchida AM, Garber JJ, Stephansson O, Söderling J, Roelstraete B, et al. Pregnancy Outcomes in Females with Eosinophilic Esophagitis: A Nationwide Population-Based Study. Inflamm Intest Dis. 2023;8:143-52.
37. Huang J, White AA. Symptoms and treatment of eosinophilic esophagitis prior to, during, and after pregnancy. J Allergy Clin Immunol Pract. 2024;12:1931-2.e2.
38. US Food and Drug Administration. Xolair (Omalizumab): full prescribing information/Supplement SUPPL-5245, 2024 [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/103976s5245lbl.pdf . Accessed on Jul 7 2024.
39. US Food and Drug Administration. Dupilumab full prescribing information/ Supplement SUPPL 59 (2024) [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761055s059lbl.pdf. Accessed on Aug 7 2024.
40. US Food and Drug Administration. Mepolizumab full prescribing information/ Supplement SUPPL 21 (2023) [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125526Orig1s021,761122Orig1s011Corrected_lbl.pdf. Accessed on Aug 7 2024.
41. US Food and Drug Administration full prescribing information/ Supplement SUPPL 20 (2024) [Internet]. Available from: https://www. accessdata. fda. gov/drugsatfda_docs/label/2024/761070Orig1s020correctedlbl.pdf. Accessed on Aug 7 2024.
42. US Food and Drug Administration. Tezepelumab full prescribing information/ Supplement SUPPL-3 [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761224s003lbl.pdf. Accessed on Aug 7 2024.
43. US Food and Drug Administration. Reslizumab full prescribing information/ Supplement SUPPL 10 (2019) [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/0761033s010lbl.pdf. Accessed on Aug 07 2024.
44. US Food and Drug Administration. Tralokinumab full prescribing information/ Supplement SUPPL 6 (2024) [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761180s006lbl.pdf. Accessed on Aug 7 2024.
45. US Food and Drug Administration. Abrocitinib full prescribing information/ Supplement SUPPL 4 (2023) [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/213871s004lblcorrected.pdf. Accessed on Aug 7 2024.
46. US Food and Drug Administration. Upadacitinib full prescribing information/ Supplement SUPPL 22 [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211675s000lbl.pdf. Accessed on Aug 7 2024.
47. US Food and Drug Administration. Baricitinib full prescribing information/ Supplement SUPPL 7 (2022) [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207924s007lbl.pdf. Accessed on Aug 7 2024.
48. US Food and Drug Administration. Ruxolitinib (OPZELURA) full prescribing information/ Supplement SUPPL 4 (2023) [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215309Orig1s000correctedlbl.pdf. Accessed on Aug 7 2024.
49. Novartis Biociencias S.A. Xolair® (omalizumabe) Bula profissional [Internet]. Available from: https://consultas.anvisa.gov.br/#/bulario/q/?nomeProduto=Xolair. Accessed on Aug 13 2024.
50. Sanofi Medley Farmacêutica Ltda. Dupixent® (dupilumabe). Bula profissional [Internet]. Available from: https://consultas.anvisa.gov.br/#/bulario/q/?nomeProduto=Dupixent. Accessed on Aug 13 2024.
51. Glaxosmithkline Brasil Ltda. Nucala (Mepolizumabe). Bula profissional [Internet]. Available from: https://consultas.anvisa.gov.br/#/bulario/q/?nomeProduto=Nucala. Accessed on Aug 13 2024.
52. Astrazeneca do Brasil Ltda. Fasenra® Pen (benralizumabe). Bula do profissional [Internet]. Available from: https://consultas.anvisa.gov.br/#/bulario/q/?nomeProduto=Fasenra. Accessed on Aug 13 2024.
53. Astrazeneca do Brasil Ltda. Tezspire® tezepelumabe. Bula do profissional [Internet]. Available from: https://consultas.anvisa.gov.br/#/bulario/q/?nomeProduto=TEZSPIRE. Accessed on Aug 13 2024.
54. Pfizer Brasil Ltda. CIBINQO® abrocitinibe. Bula do profissional [Internet]. Available from: https://consultas.anvisa.gov.br/#/bulario/q/?nomeProduto=CIBINQO. Accessed on Aug 13 2024.
55. Abbvie Farmacêutica Ltda. RINVOQ® (upadacitinibe). Bula do profissional [Internet]. Available from: https://consultas.anvisa.gov.br/#/bulario/q/?nomeProduto=Rinvoq. Accessed on Aug 13 2024.
56. Eli Lilly do Brasil Ltda. Olumiant® (baricitinibe). Bula do profissional [Internet]. Available from: https://consultas.anvisa.gov.br/#/bulario/q/?nomeProduto=Olumiant. Accessed on Aug 13 2024.
57. Global Initiative for Asthma. 2024 GINA Main Report. Global Strategy for Asthma Management and Prevention [Internet]. Available from: https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf. Accessed on Jul 6 2024.

58. Naftel J, Jackson DJ, Coleman M, d'Ancona G, Heaney LG, Dennison P, et al. An international consensus on the use of asthma biologics in pregnancy. Lancet Respir Med. 2025 Jan;13(1):80-91.

59. Sarinho FW, Rubini N de PM, Costa AJF, Silva EC de F, Monteiro FP, Serpa FS, et al. Guia prático para o uso de imunobiológicos em doenças alérgicas - ASBAI. Arq Asma Alerg Imunol. 2023;7(4): 339-66. doi 10.5935/2526-5393.20230054.

60 Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Resolução da Diretoria Colegiada – RDC N° 60, de 17 de dezembro de 2010 [Internet]. Available from: https://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2010/rdc0060_17_12_2010.pdf. Accessed on Aug 13 2024.

61. Namazy J, Cabana MD, Scheuerle AE, Thorp JM Jr, Chen H, Carrigan G, et al. The Xolair Pregnancy Registry (EXPECT): the safety of omalizumab use during pregnancy. J Allergy Clin Immunol. 2015;135:407-12.

62. Namazy JA, Blais L, Andrews EB, Scheuerle AE, Cabana MD, Thorp JM, et al. Pregnancy outcomes in the omalizumab pregnancy registry and a disease-matched comparator cohort. J Allergy Clin Immunol. 2020;145:528-36.e1.

63. Gemicioglu B, Yalçın AD, Havlucu Y, Karakaya G, Özdemir L, Keren M, et al. Country-based report: the safety of omalizumab treatment in pregnant patients with asthma. Turk J Med Sci. 2021;51:2516-23.

64. Patruno C, Guarneri F, Nettis E, Bonzano L, Filippi F, Ribero S, et al. Safety of omalizumab in chronic urticaria during pregnancy: a real-life study. Clin Exp Dermatol. 2024;49:344-7.

65. Namazy J, Scheuerle A, Spain V, Janampally P, Ahmed A, Gupta S, et al. Pregnancy and infant outcomes among pregnant women with Chronic Spontaneous Urticaria (CSU) treated with omalizumab: a descriptive analysis from the EXPECT pregnancy registry. J Allergy Clin Immunol. 2021;147:AB145.

66. Majou D, Moreira B, Martin C, Chhun S, Treluyer JM, Tsatsaris V, et al. Safety of Omalizumab During Pregnancy and Breast-Feeding With Assessment of Placental Transfer: A Case Report. Allergy Asthma Immunol Res. 2021;13:515-6.

67. Kuprys-Lipinska I, Tworek D, Kuna P. Omalizumab in pregnant women treated due to severe asthma: two case reports of good outcomes of pregnancies. Postepy Dermatol Alergol. 2014;31:104-7.

68. Hirashima J, Hojo M, Iikura M, Hiraishi Y, Nakamichi S, Sugiyama H, et al. [A case of an asthma patient receiving omalizumab during pregnancy]. Arerugi. 2012;61:1683-7.

69. Kuschnir F, Emerson F, Cordeiro N, Rocha MV, Filho SL, Rios JL. 273 fetal loss in severe asthma and posterior healthy pregnancy and birth with the use of omalizumab – case report. World Allergy Organ J. 2012;5:S89.

70. Liao S-L, Yu M, Zhao Z-T, Maurer M. Case Report: Omalizumab for Chronic Spontaneous Urticaria in Pregnancy. Front Immunol. 2021;12:652973.

71. Losappio LM, Mirone C, Schroeder JW, Scibilia J, Balossi L, Pastorello EA. Omalizumab Use in Chronic Spontaneous Urticaria during Pregnancy and a Four Years' Follow-Up: A Case Report. Case Rep Dermatol. 2020;12:174-7.

72. González-Medina M, Curto-Barredo L, Labrador-Horrillo M, Giménez-Arnau A. Omalizumab use during pregnancy for chronic spontaneous urticaria (CSU): report of two cases. J Eur Acad Dermatol Venereol. 2017;31:e245-6.

73. Ghazanfar MN, Thomsen SF. Successful and Safe Treatment of Chronic Spontaneous Urticaria with Omalizumab in a Woman during Two Consecutive Pregnancies. Case Rep Med. 2015;2015:368053.

74. Cuervo-Pardo L, Barcena-Blanch M, Radojicic C. Omalizumab use during pregnancy for CIU: a tertiary care experience. Eur Ann Allergy Clin Immunol. 2016;48:145-6.

75. Schoder K, Zhu Y, Schneeweiss S, Merola JF, Savage TJ, Gibbs LR, et al. Use of systemic immunomodulating medications in pregnant women with atopic dermatitis: A nationwide US study. J Am Acad Dermatol. 2023;89:178-81.

76. Avallone G, Cavallo F, Tancredi A, Maronese CA, Bertello M, Fraghì A, et al. Association between maternal dupilumab exposure and pregnancy outcomes in patients with moderate-to-severe atopic dermatitis: A nationwide retrospective cohort study. J Eur Acad Dermatol Venereol. 2024 Sep;38(9):1799-808.

77. Khamisy-Farah R, Damiani G, Kong JD, Wu J-H, Bragazzi NL. Safety profile of Dupilumab during pregnancy: a data mining and disproportionality analysis of over 37,000 reports from the WHO individual case safety reporting database (VigiBaseTM). Eur Rev Med Pharmacol Sci. 2021;25:5448-51.

78. Di Lernia V, Peccerillo F. Long-Term Follow-Up of Dupilumab Treatment During Conception, Pregnancy and Lactation. Indian J Dermatol. 2024;69:193-5.

79 Alvarenga JM, Maria Lé A, Torres T. Dupilumab for Atopic Dermatitis During Pregnancy and Breastfeeding: A Case Report. Actas Dermosifiliogr. 2024 Nov-Dec;115(10):1100-1102.

80. Akhtar NH, Khosravi-Hafshejani T, Akhtar D, Dhadwal G, Kanani A. The use of dupilumab in severe atopic dermatitis during pregnancy: a case report. Allergy Asthma Clin Immunol. 2022;18:9.

81. Costley M, Murphy B. Severe atopic dermatitis treated successfully with dupilumab throughout pregnancy. Clin Exp Dermatol. 2022;47:960-1.

82. Gracia-Darder I, Pons De Ves J, Reyero Cortina M, Martín-Santiago A. Patient with atopic dermatitis, hyper IgE syndrome and ulcerative colitis, treated successfully with dupilumab during pregnancy. Dermatol Ther. 2022;35:e15237.

83. Kage P, Simon J-C, Treudler R. Case of atopic eczema treated with dupilumab throughout conception, pregnancy, and lactation. J Dermatol. 2021;48:E484-5.

84. Lobo Y, Lee RC, Spelman L. Atopic Dermatitis Treated Safely with Dupilumab during Pregnancy: A Case Report and Review of the Literature. Case Rep Dermatol. 2021;13:248-56.

85. Mian M, Dunlap R, Simpson E. Dupilumab for the treatment of severe atopic dermatitis in a pregnant patient: A case report. JAAD Case Rep 2020;6:1051-2.

86. Hong N, Park SY, Kook HD, Lee DH, Jung HJ, Park MY, et al. Atopic dermatitis treated safely with dupilumab during pregnancy and lactation: A case series of four patients. Australas J Dermatol. 2024;65:e100-3.

87. Bosma AL, Gerbens LAA, Middelkamp-Hup MA, Spuls PI. Paternal and maternal use of dupilumab in patients with atopic dermatitis: a case series. Clin Exp Dermatol. 2021;46:1089-92.

88. Escolà H, Figueras-Nart I, Bonfill-Orti M, Coll Puigserver N, Martin-Santiago A, Rodríguez Serna M, et al. Dupilumab for atopic dermatitis during pregnancy and breastfeeding: Clinical experience in 13 patients. J Eur Acad Dermatol Venereol. 2023;37:e1156-60.

89. Vittorakis SK, Giannakopoulou G, Samitas K, Zervas E. Successful and safe treatment of severe steroid depended eosinophilic asthma with mepolizumab in a woman during pregnancy. Respir Med Case Rep. 2023;41:101785.

90. Ozden G, Pınar Deniz P. May mepolizumab used in asthma correct subfertility? Ann Med. 2021;53:456-8.

91. Naftel J, Eames C, Kerley S, Whitfield C, Rayala-Montaniel E, Cook P, et al. Benralizumab treatment of severe asthma in pregnancy: A case series. J Allergy Clin Immunol Pract. 2023;11:2919-21.

92. Saco T, Tabatabaian F. Breathing for two: a case of severe eosinophilic asthma during pregnancy treated with benralizumab. Ann Allergy Asthma Immunol. 2018;121:S92.

93. Adbry® (tralokinumab-ldrm). MotherToBaby 2022 [Internet]. Available from: https://mothertobaby.org/ongoing-study/adbry-tralokinumab/ . Accessed on Jul 8 2024.

94. Adam DN, Gooderham MJ, Beecker JR, Hong CH, Jack CS, Jain V, et al. Expert consensus on the systemic treatment of atopic dermatitis in special populations. J Eur Acad Dermatol Venereol. 2023;37:1135-48.

95. Kammerer S. No adverse pregnancy outcomes in patients exposed to baricitinib. In: van de Kerkhof P, editor. Medicom Conference Report SPIN 2022. Baarn, the Netherlands: Medicom Medical Publishers; 2022. doi 10.55788/3f9a9e76.

No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Marcelo Vivolo Aun
E-mail: marcelovivoloaun@gmail.com