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Safety of biologics for atopic diseases during pregnancy

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Abstract

The high prevalence of atopic diseases in women of childbearing age reveals the need to determine the safety of biologics during pregnancy. This review summarizes the effects of seven FDA-approved biologics (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab, and tralokinumab) on maternal and fetal outcomes. For this purpose, we reviewed English-language publications to investigate whether the use of biologics for atopic diseases during pregnancy increased the risk of preterm delivery, stillbirth, low birth weight, or congenital malformations. Most publications found were case reports, case series, or observational studies reporting outcomes in a total of 313 pregnancies. No randomized controlled studies were identified. We found that biologics do not seem to influence maternal or fetal outcomes. Indeed, worsening of the underlying atopic disease during pregnancy appears to be more detrimental to the viability of the pregnancy. Given the small sample size and scarcity of studies, future research should include prospective studies with comparable control groups without exposure to biologics and multicenter registries for long-term follow-up.

Keywords

Atopic diseases; asthma; chronic urticaria; atopic dermatitis; safety; pregnancy; preterm; stillbirth; birth weight; congenital malformations; biologics; omalizumab; mepolizumab; reslizumab; benralizumab; dupilumab; tezepelumab; tralokinumab

Introduction

Atopic diseases are highly prevalent in women of childbearing age, affecting up to 30% of women in this age group (1). New onset or worsening of preexisting atopic diseases may occur during pregnancy, which can be detrimental to the viability of the pregnancy. Therefore, optimizing the medical treatment of atopic diseases is imperative for favorable pregnancy outcomes.

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Several studies have linked poorly controlled asthma with unfavorable pregnancy outcomes. For instance, a meta-analysis published in 2011 summarized the literature between 1975 and 2009 concerning the risks of adverse maternal and fetal outcomes in women with asthma. This study revealed that maternal asthma was associated with an increased risk of low birth weight, small size for gestational age, preterm delivery, and preeclampsia. This same study demonstrated that active asthma management reduced the relative risk of preterm labor and delivery to non-significant levels (2). Another meta-analysis published in 2013 showed that maternal asthma was associated with a significantly increased risk of congenital malformations, cleft lip with or without cleft palate, neonatal death, and neonatal hospitalization (3). As such, these studies indicate that the benefit of active treatment to maintain asthma control and prevent exacerbations outweighs the potential risks of medications. The effects of other atopic diseases on maternal or fetal outcomes are less known.

Biologics have revolutionized the management of atopic diseases, with more patients achieving remission from active disease. Biologics are considered when conventional treatments are poorly tolerated or ineffective. Biologics were first approved for asthma, followed by chronic urticaria, atopic dermatitis, eosinophilic granulomatosis with polyangiitis (EGPA), chronic rhinosinusitis with nasal polyps, and hypereosinophilic syndrome (HES). There are currently seven biologics approved for atopic diseases, including omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab, and tralokinumab. Notably, the randomized clinical trials (RCT) that served as the basis for the United States (US) Food and Drug Administration (FDA) approvals of these medications commonly excluded pregnant women. Thus, the applicability of data regarding the safety and efficacy of these biologics when used in pregnant women is largely unknown.

In this article, we reviewed the available English-language literature to investigate if the use of biologics during pregnancy increases the risk of preterm delivery, stillbirth, low birth weight, or congenital malformations. The articles included in our review are summarized in Table 1.

Omalizumab

Omalizumab is a monoclonal humanized IgG1 antibody that binds to IgE heavy chain and prevents its binding to receptors on mast cells and basophils, which dampens the release of proinflammatory mediators and blunts the downstream allergic response (4). Like other IgG molecules, omalizumab crosses the placenta during the second and third trimesters (5). Omalizumab was first approved by the FDA for severe asthma in 2003, followed by chronic idiopathic urticaria in 2014.

In 2019, the European Public Assessment Report (EPAR) and the European Medicines Agency (EMA) stated that omalizumab could be considered for asthma treatment during pregnancy. The currently published consensus does not recommend the initiation of omalizumab during pregnancy. However, if a woman becomes pregnant while receiving omalizumab, it is suggested that therapy can be continued if the benefits are estimated to outweigh the potential harms (6).

To our awareness, there are no published RCT involving omalizumab use during pregnancy. Clinical data for the safety of omalizumab during pregnancy in women with atopic disease mainly involve case reports, case series, and one pregnancy registry. In a reproduction study, no evidence of fetal harm was observed in cynomolgus monkeys with a subcutaneous dose of omalizumab up to five times the maximum recommended human dose (7).

Omalizumab and asthma

The Observational Study of the Use and Safety of Xolair (omalizumab) during Pregnancy (EXPECT), conducted in the US from 2006 to 2018, is the largest prospective study on this subject. It reported outcomes in 230 pregnant women with asthma exposed to omalizumab eight weeks prior to or anytime during pregnancy. This study identified a congenital anomaly rate of 8.1%, a live birth rate of 99.1%, a stillbirth rate of 0.9%, and a preterm delivery rate of 15.0% in this cohort. Registry findings were compared to the age-adjusted disease-matched cohort of 1,153 pregnant women with asthma and without exposure to omalizumab, called the Quebec External Comparator Cohort (QECC). This comparison revealed that the rate of live births and the prevalence of major congenital malformation were similar to that of the EXPECT sub-cohort. There was an increased rate of low birth weight in infants among patients who had received omalizumab (13.7% in EXPECT versus 9.8% in QECC). However, 64.9% of women in the EXPECT sub-cohort had severe asthma compared to 21.2% in QECC, which makes it difficult to establish whether the low birth weight was due to drug exposure or disease severity (8, 9). It is worth mentioning that, in the US general population, the estimated background risk of birth defects is approximately 3%, stillbirth 0.625%, preterm birth 10.1%, and low birth weight 8.24% (10, 11).

A case study from Turkey analyzed the data from 20 women with a history of asthma who were exposed to omalizumab pre-conception or during pregnancy. These 20 women were retrospectively evaluated using a questionnaire regarding their disease and therapy and the health of their infants. One patient gave birth to twins, two patients to two infants each in different years, and 17 to one infant each. Three infants (13%) had low birth weight, and five infants (21.7%) were born prematurely. No congenital anomalies were detected. Seven (30.4%) infants developed atopic diseases (12).

Furthermore, we reviewed five case reports describing the outcomes of six women who had a history of severe asthma that improved on omalizumab therapy. All of them were exposed to omalizumab during the first trimester or throughout pregnancy. Importantly, all pregnancies led to live births. No congenital abnormalities were observed. There were two premature births, and one infant had low birth weight (13-17). These findings were not unexpected given their asthma severity before initiation of omalizumab therapy.

Omalizumab and chronic urticaria

A descriptive analysis from the EXPECT registry on pregnancy and infant outcomes in women with chronic spontaneous urticaria treated with omalizumab was recently presented at the 2021 American Academy of Allergy, Asthma & Immunology (AAAAI) annual meeting. This analysis revealed that there were 37 patients enrolled in the registry who had a diagnosis other than asthma. Of the 37 patients, 30 had a diagnosis of chronic

idiopathic urticaria (CIU). All 30 patients were exposed to omalizumab at least during the first trimester. The analysis identified a spontaneous abortion rate of 3%, premature birth rate of 13%, and major congenital anomalies rate of 7%. Overall, the results were comparable to that of patients with asthma in EXPECT (18).

Additionally, we reviewed six case reports and one case series describing the outcomes in twelve pregnant women who used omalizumab for chronic refractory urticaria. All twelve women were exposed to omalizumab during the first trimester of pregnancy. Two of the twelve women discontinued therapy for fear of potential fetal harm. However, one of the two patients experienced a severe disease exacerbation, which prompted the resumption of omalizumab. Two women conceived twice during omalizumab therapy. All pregnancies showed a normal progression and delivered live, normal-weight infants at term. No congenital abnormalities were reported (19-24). Five of the 14 children were followed and remained developmentally normal (21, 23, 24).

Mepolizumab

Mepolizumab is a humanized IgG1 monoclonal antibody that inhibits the interleukin-5 (IL-5) by blocking its binding to the IL-5 receptor expressed on eosinophils, thereby reducing the production and survival of eosinophils (25). Mepolizumab was first approved by the FDA in 2015 as an add-on therapy for severe asthma. It was subsequently approved for eosinophilic granulomatosis with polyangiitis (EGPA) in 2017 and for hypereosinophilic syndrome (HES) in 2020. There are no published RCT on pregnancy exposure to mepolizumab. There is one ongoing pregnancy exposure registry on mepolizumab, which is estimated to be completed in 2023 (26). A prenatal and postnatal developmental study conducted in cynomolgus monkeys showed no evidence of fetal harm with intravenous (IV) mepolizumab at doses nine times the maximum recommended human dose (27).

We reviewed a case study that reported outcomes in two women who became pregnant while on mepolizumab therapy for severe asthma. Both women conceived after two doses of mepolizumab. One woman decided to terminate the pregnancy due to the unknown effects of mepolizumab on pregnancy. The other woman decided to hold mepolizumab therapy and continue with her pregnancy. She delivered a healthy child at term without congenital abnormalities (28).

Benralizumab

Benralizumab is a humanized IgG1 monoclonal antibody that inhibits IL-5. By blocking IL-5 activity, it reduces the production and activation of eosinophils, which are one of the primary mediators of inflammation in allergic asthma and nonallergic forms of asthma with prominent eosinophilia (29). Benralizumab was approved by the FDA in 2017 for the treatment of severe asthma. There are no published RCT on pregnancy exposure to benralizumab. An ongoing benralizumab pregnancy exposure study is in the recruitment phase and is expected to be completed in 2026 (30). Animal developmental studies did not show evidence of fetal harm when cynomolgus monkeys received IV benralizumab at a dose

310 times the maximum recommended human dose. Eosinophil counts were suppressed in infant monkeys with subsequent gradual recovery (31).

We reviewed two case reports regarding the pregnancy outcomes in two women exposed to benralizumab during pregnancy. The first woman was on benralizumab for hypereosinophilic syndrome and severe eosinophilic gastrointestinal involvement. The patient delivered a healthy, normal-weight girl at 38 weeks. Post-delivery, the newborn's eosinophil counts were undetectable for seven months. The one-year follow-up revealed normal growth and development without any sick visits or atopic disorders (32). The second woman was on benralizumab for severe eosinophilic asthma. She discontinued the benralizumab when she conceived; however, she resumed benralizumab therapy at 20 weeks' gestation due to severe exacerbations. The authors reported improvement in asthma control, eosinophilia, and lower extremity edema with limited fetal complications. No further information on fetal outcomes was provided (33).

Reslizumab

Reslizumab is a humanized monoclonal antibody (IgG4), which blocks IL-5 signaling, thereby reducing the production and survival of eosinophils and downstream eosinophilic-driven inflammation (34). Reslizumab was approved by the FDA in 2016 as an add-on maintenance therapy for severe asthma with an eosinophilic phenotype. To our knowledge, there are no published human data during pregnancy, and therefore, the potential risks on maternal and fetal outcomes are unknown in humans. Reproductive studies in pregnant mice and rabbits exposed to IV reslizumab at six times and seventeen times the maximum recommended human dose, respectively, did not show evidence of embryo-fetal developmental effects (35).

Dupilumab

Dupilumab is a monoclonal humanized IgG4 antibody which binds to the interleukin-4 receptor alpha subunit (IL-4Rα). IL-4Rα is also part of the IL-13 receptor. Thus, dupilumab blocks the effects of IL-4 and IL-13, both known mediators of atopic dermatitis (36). Dupilumab was first approved by the FDA for eczema or atopic dermatitis in 2017. Subsequently, FDA approved dupilumab for the treatment of moderate-to-severe eosinophilic asthma in 2018 and inadequately controlled chronic rhinosinusitis with nasal polyps in 2019. There are no published RCT regarding dupilumab exposure during pregnancy. There are currently two observational studies aiming to evaluate pregnancy outcomes after dupilumab use. These studies are currently in the recruitment phase and are estimated to be completed in 2026 and 2027, respectively (37, 38). In an enhanced prenatal and postnatal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous dupilumab at doses up to ten times the maximum recommended human dose(39).

We reviewed seven case reports evaluating the consequences in seven women and their offspring who were exposed to dupilumab during pregnancy. Six women were on dupilumab for atopic dermatitis, while one received this biologic for the treatment of pemphigoid

gestationis. All seven pregnancies led to live births. There was one premature birth, while another infant had low birth weight (40-47). Furthermore, data presented in a different case series suggested that paternal use of dupilumab does not impact male fertility and fetal outcomes (48).

Tezepelumab

Tezepelumab is a humanized IgG2 monoclonal antibody that inhibits the action of thymic stromal lymphopoietin, an epithelial cell-derived cytokine involved in the pathogenesis of asthma (49). Tezepelumab received its first approval by the FDA in December 2021 as an add-on therapy for severe asthma. There are no available published human data on tezepelumab exposure during pregnancy to evaluate any drug-associated risk of adverse maternal and fetal outcomes. In an animal developmental study in cynomolgus monkeys, placental transport of tezepelumab was observed, but there was no evidence of fetal harm following IV administration of tezepelumab throughout pregnancy (50).

Tralokinumab

Tralokinumab is a humanized IgG4 monoclonal antibody, which binds to and neutralizes the effect of IL-13, thereby preventing its interaction with IL-13 receptors and subsequent downstream signaling (51). Tralokinumab was first approved by the FDA in December 2021 for moderate to severe atopic dermatitis. Additional studies are needed to determine the effects of tralokinumab on pregnancy and fetal outcomes. In an enhanced developmental study, the administration of IV tralokinumab to pregnant monkeys did not result in adverse developmental effects in their offspring (52).

Discussion

In summary, we reviewed 25 non-randomized studies (2 cohort studies and 23 case reports/series). Our search did not reveal randomized controlled trials involving biologics for atopic diseases during pregnancy. In total, all publications reported 313 exposures to biologics prior to/at conception or during pregnancy. Among the 313 pregnancies, 311 were maternal exposure, while 2 were paternal exposures. Medical indications for biologic exposure were asthma, chronic urticaria, atopic dermatitis, eosinophilic granulomatosis polyangiitis, hypereosinophilic syndrome, and pemphigoid gestationis.

This review suggests that women who inadvertently become pregnant while taking biologics can be reassured that continuing these therapies does not appear to impose an increased risk to themselves or their children. However, it is important to note that among the 313 pregnancies reviewed, 298 describe the outcomes after exposure to omalizumab. Among the remaining 15 pregnancies, 11 were exposed to dupilumab, 3 to mepolizumab, and 1 to benralizumab. There were no published human pregnancy data on reslizumab, tezepelumab, or tralokinumab. Therefore, there is insufficient data for most biologics to make a firm conclusion about drug-associated risks. We should also keep in mind that biologics are more commonly used in patients with severe disease activity, which might influence pregnancy outcomes, especially if patients are not compared with pregnant women with

a similar degree of disease severity treated without biologics. Therefore, in these instances, it may become difficult to establish whether maternal or fetal abnormalities are due to the medication or the severity of the underlying disease. Finally, many reports lacked information on maternal age, disease activity, birth weights, co-morbidities, or concomitant medications.

Importantly, this review revealed that one woman decided to terminate her pregnancy after biologic exposure and several women stopped effective biologic therapy due to unknown effects of medication on their pregnancies. Unfortunate outcomes like these suggest the strong need for future research. Future studies assessing these maternal and fetal outcomes should be prospective and include comparable women with similar disease severity but without exposure as a control group to draw a firm conclusion. Furthermore, the long-term implications of fetal exposure to biologics in the uterus should be conducted, especially to elucidate the risk of therapy on the neonatal immune system.

Due to the practical and ethical challenges of interventional studies in this patient group, we emphasize the importance of specialists publishing any cases that become available. As more biologics are approved for the management of atopic diseases, we encourage allergists and other specialists to enroll their pregnant patients with exposure to these medications in the ongoing national or international registries. These include registries for mepolizumab (https://mothertobaby.org/ongoing-study/nucala-mepolizumab/), benralizumab (https://mothertobaby.org/ongoing-study/fasenra-benralizumab/). and dupilumab (https://mothertobaby.org/ongoing-study/dupixent-dupilumab%e2%80%8e/).

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Abbreviations:

RCT	Randomized controlled trials
FDA	Food and Drug Administration
RR	relative risk
IL	interleukin
EPAR	European Public Assessment Report
EMA	European Medicines Agency
EXPECT	Observational Study of the Use and Safety of Xolair (omalizumab) during Pregnancy
QECC	Quebec External Comparator Cohort

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Table 1.

Characteristics of studies included in the review.

	Medication	Disease	Study design	Timing of exposure	Number of patients exposed	Live births	Major birth defects	Low birth weight	Preterm births	Stillbirths
1	Omalizumab	Asthma	The Observational Study of the Use and Safety of Xolair (omalizumab) During Pregnancy (EXPECT) (Namazy, Blais et al. 2020) [8, 9]	246 patients were exposed during first trimester	230	233 (99.1%) (223 singletons and 10 twins)	(8.1%)	(13.7%)	(15%)	2 (0.9%)
2		Asthma	Retrospective case study (Gemicioğlu, Yalçin et al. 2021) [12]	Variable	20	23 (2 twins)	0	3	5	0
3		Asthma	Case reports (Kupryś-Lipińska, Tworek et al. 2014) [13]	Throughout pregnancy	2	2	0	0	0	0
4		Asthma	Case report (Hirashima, Hojo et al. 2012) [14]	First trimester	1	1	0	1	1	0
5		Asthma	Case report (Kuschnir, Emerson et al. 2012) [15]	First trimester	1	1	0	0	0	0
6		Asthma	Case report (Cortese, Di Lizia et al. 2013) [16]	First trimester	1	1	0	NA	1	0
7		Asthma	Case report (Majou, Moreira et al. 2021) [17]	Throughout pregnancy	1	1	0	0	0	0
8		CIU	Observational study (EXPECT) (Namazy, J., 2021) [18]	First trimester	30	29	2	1	4	0
9		CIU	Case report (Cuervo-Pardo, Barcena-Blanch et al. 2016) [19]	Throughout pregnancy	4	4	0	0	0	0
10		CIU	Case report (Liao, Yu et al. 2021) [20]	Variable	2	2	0	0	0	0
11		CIU	Case report (Losappio, Mirone et al. 2020) [21]	Throughout pregnancy	1	1	0	0	0	0
12		CIU	Case report (Ensina, Cusato-Ensina et al. 2017) [22]	Variable	2	3 (2 twins)	0	0	0	0
13		CIU	Case report (Ghazanfar and Thomsen 2015) [23]	Throughout pregnancy	1	2 (conceived twice)	0	0	0	0
14		CIU	Case report (Gonzalez-Medina, Curto-Barredo et al. 2017) [24]	Variable	2	2	0	0	0	0
15	Mepolizumab	Asthma	Case report (Ozden and Pinar Deniz 2021) [28]	First trimester	2	1	0	0	0	0

J Allergy Clin Immunol Pract. Author manuscript; available in PMC 2023 December 01.

	Medication	Disease	Study design	Timing of exposure	Number of patients exposed	Live births	Major birth defects	Low birth weight	Preterm births	Stillbirths
16		Severe eosinophilic granulomatosis with polyangiitis	Case report (Kasuya, Kitano et al. 2019) *	Exposed after delivery	1	N/A (Due to time of exposure)	N/A	N/A	N/A	N/A
17	Benralizumab	Hypereosinop hilic syndrome with severe eosinophilic gastrointestin al involvement	Case report (Manetz, Marie et al. 2021) [32]	Throughout pregnancy	1	1	0 (0 eosinophil count at birth to 7 months)	0	0	0
18		Asthma	Case report (Saco and Tabatabaian 2018) [33] **	Third trimester	N/A	N/A	N/A	N/A	N/A	N/A
19	Dupilumab	Atopic dermatitis	Case series (Bosma, Gerbens et al. 2021) [48]	2 men at conception 2 women prior to conception	4	4	0	0	0	0
20		Atopic dermatitis	Case report (Lobo, Lee et al. 2021) [40]	First and second trimester	1	1	0	0	0	0
21		Atopic dermatitis	Case report (Kage, Simon et al. 2020, Kage, Simon et al. 2021) [41, 42]	Throughout pregnancy	1	1	0	0	0	0
22		Atopic dermatitis	Case report (Mian, Dunlap et al. 2020) [43]	Third trimester	1	1	0	0	0	0
23		Atopic dermatitis	Case report (Gracia-Darder, Pons De Ves et al. 2021) [44]	Throughout pregnancy	1	1	0	0	0	0
24		Atopic dermatitis	Case report (Costley and Murphy 2021) [45]	Throughout pregnancy	1	1	0	0	0	0
25		Atopic dermatitis	Case report (Akhtar, Khosravi-Hafshejani et al. 2022) [47]	Throughout pregnancy	1	1	0	1	0	0
26		Pemphigoid gestationis	Case report (Riquelme-McLoughlin and Mascaró 2021) [46]	Third trimester	1	1	0	N/A	1	0
Total					313	318	21	38	47	2

N/A = Not available/Not applicable

CIU = Chronic idiopathic urticaria

* Mepolizumab was given after the delivery. Therefore, pregnancy outcomes could not be attributed to mepolizumab use.

** Exposed to benralizumab during pregnancy. However, no further information on fetal outcomes was provided.