

Omalizumab safety in pregnancy



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The study by Namazy et al¹ addressing the important clinical question of the safety of omalizumab (Xolair; Genentech, South San Francisco, Calif) for the mother and fetus when treating asthma during pregnancy is the result of a postmarketing commitment, of the manufacturing company to the US Food and Drug Administration (FDA). Omalizumab is a recombinant IgG₁ anti-IgE mAb used as an add-on drug in patients with moderate-to-severe allergic asthma whose symptoms are not well controlled by other medications.² In the current study (the Xolair Pregnancy Registry [EXPECT]) maternal and neonatal outcomes of women with moderate-to-severe asthma treated with conventional drugs and omalizumab during pregnancy were compared with those of a group of asthmatic women treated with conventional drugs but not treated with omalizumab.

The initial results of the EXPECT study, published in the *Journal* in 2015,³ reported 169 pregnancies exposed to omalizumab with known outcomes. Importantly, the current publication reports on an additional 61 maternal and pregnancy outcomes for a total of 230 pregnant women exposed to omalizumab. This is in comparison with an external non-omalizumab-exposed cohort of 1153 disease-matched women (moderate-to-severe asthma) created using information from health care databases in Quebec, Canada. The authors conclude that they did not detect evidence of an increased risk of major congenital anomalies in the omalizumab-treated group.

Omalizumab binds to the Fc (Cε3) of free IgE antibodies. This inhibits the interaction between IgE and FcεRI, preventing mast cell and basophil activation and subsequently downregulating the receptors over time. Omalizumab also blocks IgE binding to CD23 on B cells, platelets, and antigen-presenting cells (Fig 1).

Omalizumab has a good safety profile, showing usually mild-to-moderate adverse events typical of other biologics, such as injection-site reactions, headache, fever, and upper respiratory

tract symptoms. Infrequently, anaphylaxis occurs, and in rare instances there is an increased risk of parasitic infection.

Asthma during pregnancy is common, affecting approximately 3.3% to 5.8% of women.⁴ In the present study 16.5% of patients had moderate asthma during pregnancy, and 19% had the severe form. Drug therapy for asthma during pregnancy includes the treatment of acute exacerbations of an asthma attack, as well as maintenance therapy for long-term control. Several medications are used during pregnancy in a stepwise fashion and include inhaled short-acting β₂-agonists and long-acting β₂-agonists, inhaled corticosteroids and oral corticosteroids (OCSs), inhaled long-acting antimuscarinic agents, leukotriene receptor antagonists, and theophylline. Aside from OCSs, these medications mostly have long-term safety profiles. Newer agents, such as omalizumab, anti-IL-5 (mepolizumab, reslizumab, and benralizumab), and anti-IL-4 receptor α (dupilumab) antibodies, have been approved as add-on medications for uncontrolled eosinophilic moderate-to-severe asthma yet have limited information on use during human pregnancy.²

Omalizumab is not frequently used during pregnancy in the United States.³ Conceivably, the limited safety information available during pregnancy restricts its use. Omalizumab has been studied extensively in patients with idiopathic chronic urticaria and was recently approved for this indication. Several case reports have been published about its efficacy and safety in pregnant women with idiopathic chronic urticaria.⁵

The degree of placental transfer of IgG depends on the IgG subtype, gestational age at exposure, and length of exposure. All IgG subtypes cross the placenta, whereas IgG₁ has the greatest transplacental transfer.⁶ The lowest omalizumab exposure is expected to happen during the first trimester of pregnancy (the organogenesis period) and the greatest during the third trimester. We base this assumption on placental studies of IgG that demonstrated 20% to 30% greater IgG levels in the newborn at birth than in maternal blood.⁶ The study by Namazy et al¹ includes women exposed to omalizumab during the 3 trimesters of pregnancy, which is a definite merit of the study.

Human isolated perfused placental cotyledon is an established model for *in vitro* drug placental transfer evaluation. Therefore we suggest assessing omalizumab transport in the human placenta in this system, followed by testing the level of omalizumab in cord blood of women using the medication in the third trimester of pregnancy. Interestingly, even if IgE itself does not cross the placenta, it feasibly does cross as a complex with IgG-anti-IgE through neonatal Fc receptor-mediated transcytosis (Fig 1).⁷ It is noteworthy that other antibody-based drugs used in asthmatic patients, such as anti-IL-5 and anti-IL-4 receptor α, will possibly raise similar issues of transplacental delivery as those raised by omalizumab.

Moderate-to-severe asthma during pregnancy can have adverse effects on pregnancy, such as increased risk of preeclampsia, small-for-gestational-age status, low birth weight, emergency cesarean section, and increased risk for preterm delivery.⁸ Furthermore, malformations, such as spina bifida, cleft lip, major

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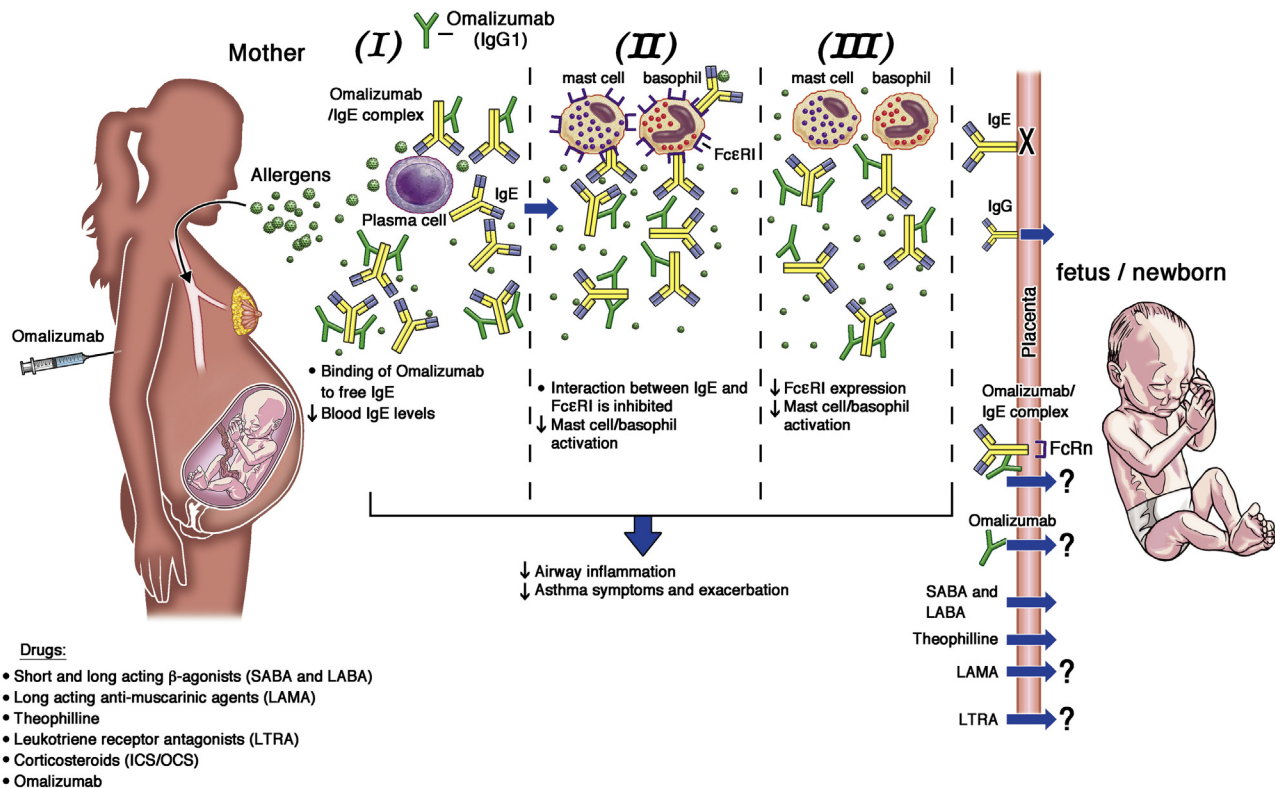


FIG 1. Omalizumab in pregnant asthmatic women. The EXPECT study was performed on pregnant women with moderate-to-severe asthma who were treated stepwise with the indicated drugs and injection of omalizumab (left). Center, The mechanism of action of omalizumab resulting in control of asthma (I, II, and III). Right, The placenta is shown, indicating transplacental crossing of omalizumab, the omalizumab-IgE complex, and other drugs. Question marks indicate that human studies are not available.

cardiac anomalies, esophageal atresia, gastroschisis, and anorectal atresia, have been reported, with varying increased odds ratios.⁹ The current study found congenital anomaly rates of 8.1% and 8.9% in the EXPECT and Quebec groups, respectively, with no apparent difference in the omalizumab-treated women.

Other studies on pregnant asthmatic patients using medications show a slightly increased rate of fetal malformation (odds ratio, 1.11)¹⁰ yet not close to the high rate of malformation found in both populations in the first study by Namazy et al (>8%).¹ This can be explained by the fact that both the EXPECT and the Quebec populations (1) are sicker than the general population, (2) use several medications during pregnancy, and (3) have higher body mass indices, which are all risk factors of increased neonatal malformation rate.

Omalizumab was classified as Category B in the safety categorization of medications during pregnancy. It should be noted that the FDA is phasing out the category system. Among the safety studies of the drug, the FDA required a postmarketing pregnancy outcome, as well as neonatal platelet counts, because of findings of thrombocytopenia in nonhuman primates. Thrombocytopenia at birth or within the first month of life was reported in 1 infant (1/230 [0.4%]) in the EXPECT group and 7 (0.6%) of 1124 in the Quebec group, thus showing no significant difference of a nonfrequent clinical problem.

Prematurity should be a major outcome parameter in any future safety studies of omalizumab in pregnancy. The EXPECT study found a slightly greater rate of preterm deliveries (15.0% vs

11.3%), yet there were differences in the populations of both cohorts. It is noteworthy that the Quebec group had greater body mass indices, were older, had worse asthma parameters, and used more corticosteroids and more long-acting β -agonists. All these factors are associated with increased risk of preterm delivery that is greater in the United States general population compared with that of Canada.

Taking all these factors into account, it is unlikely that omalizumab is solely responsible for the increased risk rate of preterm delivery. However, among women taking OCSs, the prematurity rate was 32.7% in the EXPECT pregnancies compared with half that (16.2%) in the non-omalizumab-exposed Quebec group. Although the explanation for the greater rate of prematurity in women taking OCSs and omalizumab is not yet clear, one might speculate that there could be a possible synergistic adverse effect between OCSs and omalizumab. This possible effect should be further studied and confirmed because no clear mechanism has yet been suggested, and it might have important clinical implications. Thus caution is warranted.

Notably, the study shows no increased risk of thrombocytopenia in the newborn. Therefore, also based on omalizumab's clinical efficacy in the treatment and prevention of acute asthma exacerbation, it might be part of the medications used during pregnancy. However, its "safe" use during pregnancy is not completely proved because of the observational design of the study with no statistical comparisons. Therefore randomized, double-blind, placebo-controlled studies should be conducted on

omalizumab during pregnancy before complete reassurance of the drug is established. We also suggest a clinical study should include pregnant women in the second and third trimester (after the organogenesis period) and after safety is established a study on women in the first trimester should be performed.

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