REVIEW ARTICLE

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Fetal Safety of Drugs Used in the Treatment of Allergic Rhinitis

A Critical Review

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Abstract

Allergic rhinitis is the most common allergic disease. Pharmacological interventions are often not used in pregnancy because of alarming information in drug labels and patient information, even when evidence for safety exists.

Low-risk therapies could include immunotherapy, intranasal sodium cromoglycate (cromolyn sodium), beclometasone, budesonide and first-generation antihistamines. In a meta-analysis examining the safety of first-generation antihistamines in pregnancy, 200 000 first trimester exposures failed to show increased teratogenic risk. Loratadine is the most studied second-generation antihistamine (with a total patient cohort of 2147 women who were exposed) and does not appear to increase the risk of major congenital malformations; however, it has not been as well studied as the earlier antihistamines. Since desloratadine is the principal metabolite of loratadine, it can be assumed that a similar safety profile would fit for desloratadine as was described for loratadine although no direct human studies have been done.

Decongestants have not been conclusively proven to affect the fetal outcome and may be used for short-term relief when no other safer alternatives are available.

Intranasal corticosteroids have not been associated with an increase in congenital malformations in humans. Based on efficacy and the fact that there would be little systemic absorption, they can be considered a first-line treatment over oral antihistamines, decongestants and mast cell stabilisers; however, the number of controlled trials in pregnancy is limited. Intranasal corticosteroids are associated with minimal systemic effects in adults and are the most effective therapy for allergic rhinitis. Benefit-risk considerations must, therefore, be done but favour their first-line use during pregnancy.

Because fetal safety is paramount, recommendations should be based both on the safety of the drugs during pregnancy and the comparative efficacy of the agent in the treatment of the underlying condition. This review exemplifies the fact that there are many safe treatment options for the clinician when dealing with allergic rhinitis during pregnancy.

The symptoms of allergic rhinitis include itching, sneezing, rhinorrhoea and nasal congestion. It can be accompanied by symptoms in the eyes, ears and throat. Typically, there is a gradual decrease in the occurrence and severity of symptoms with age. Symptoms of allergic rhinitis develop before the age of 20 years in 80% of cases and, therefore, fetal safety data on pharmacological treatments are critical to a large number of women.[1] Allergic rhinitis is the most common allergic disease and has shown a prevalence of 42% in 6-year-old children.[1] Allergic diseases are estimated to affect 20–30% of women of childbearing age, making them the most common medical conditions to complicate pregnancy.[2,3]

In this review, we have updated our analysis published in *Drug Safety* in 1999, which examined the safety of different pharmacological interventions available to treat allergic rhinitis in pregnancy.[4] MEDLINE and EMBASE electronic databases were searched from 1966 to September 2004 to identify relevant observational studies. The keywords included the specific drug, generic and brand name, along with 'rhinitis' and 'pregnancy'. We examined fetal outcome with respect to major and minor congenital malformations. We tried to highlight the gaps of knowledge and methodological issues that may have hindered the interpretation of existing data. We decided not to include homeopathy or other alternative treatments in this review.

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1. Pathophysiology of Allergic Rhinitis

1.1 General Mechanism of Allergic Rhinitis

The fluid in the nasal mucosa contains IgA and IgE. IgE antibodies fix to the mucosal and submucosal mast cells. With the introduction of an allergen into the nose, the mucosal and submucosal mast cells generate and release mediators, such as histamine, prostaglandin D_2 and leukotrienes, that are capable of producing tissue oedema, gland stimulation, sinusoidal congestion and sensory nerve activation, as well as late-phase reactions that lead to an influx of eosinophils. The intensity of the clinical response to inhaled allergens is correlated with the antigen dose and levels of specific IgE antibodies, as well as basophilic cell mediator releasability.[4] Once sensitised to allergens, exposures can trigger events that result in the symptoms of allergic rhinitis.[1]

1.2 Allergic Rhinitis and Pregnancy

Pregnancy has been demonstrated to affect certain mediators of the immediate hypersensitivity type reaction and their modulating factors. Plasma histamine levels in women with allergic conditions have been demonstrated to be significantly lower during the first trimester of pregnancy compared with postpartum levels.[5] Despite the theoretical protective effects of these changes on the course of allergic rhinitis, the actual clinical effects are unknown. More clinically relevant, pregnancy-related hormonal changes can lead to nasal mucosal congestion. This congestion is secondary to increased circulating blood volume and increased activity of the nasal mucosal cells, resulting in swelling and increased secretions.[6]

'Vasomotor rhinitis of pregnancy' is an entity that is characterised by nasal congestion limited to the gestational period, with more prominent symptoms during the second and third trimesters of pregnancy. It is important to note that, like asthma, preexisting symptoms of chronic rhinitis may improve, worsen or remain unchanged during pregnancy. It has been reported that nasal symptoms in pregnant women who have allergic rhinitis tend to improve in 34%, worsen in 15% and remain unchanged in the remainder of the women.[7] Another common symptom related to rhinitis during pregnancy is ear fullness that is secondary to eustachian tube congestion.[4]

2. Safety Data for Pharmacological Interventions in Pregnancy

Rhinitis management may consist of allergen avoidance, pharmacological treatment or immunotherapy. The first trimester of pregnancy is the most critical time for fetal development. Most drugs are contraindicated during pregnancy by their manufacturers, based, for the most part, on the fact that there are little human data or fetal outcomes. It is only after sufficient human observational data that safety of drugs during pregnancy can be established. In the following sections, when discussing different pharmacological interventions, the rate of congenital malformations will be compared with the baseline rate of congenital malformations in the general population (1–5%, depending on the comparison group and methodology of the detection of malformations).[8] When congenital malformations have been reported, the defects are reviewed to determine whether there is a pattern that could suggest a drug effect.

2.1 Methodological Considerations

Many of the studies identified by us are quite small and have a low power to reveal a significant teratogenic effect of a drug. A number of the existing studies are too small to draw any conclusions; moreover, the quality of studies varies widely. For example, retrospective studies are likely to have poorer data collection and potential recall and reporting bias.

2.2 First-Generation Antihistamines

First-generation antihistamines are characterised by their longevity on the market and their potential for certain adverse effects. A summary of teratogenicity studies for first-generation antihistamines in humans and animals is given in table I and table II, respectively.

Several meta-analyses have been conducted by the Motherisk Program, which examined the safety of antihistamines used in the treatment of nausea and vomiting in pregnancy and other conditions and

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Table I. Summary of teratogenicity studies for first-generation antihistamines in humans

Drug	Exposed[a]	Control[b]	Relative risk (95% CI)	Reference
Brompheniramine	10/65	3238/50 217	2.34 (1.31, 4.17)[c]	8
	5/172	100/6337	1.84 (0.76, 4.46)	9
	1/34	2/34	0.50 (0.05, 5.26)	10
Chlorphenamine (chlorpheniramine)	90/1070	3158/49 212	1.2 (0.98, 1.46)[c]	8
	4/257	101/6252	0.96 (0.36, 2.6)	9
	2/61	ND	ND	11
Dexchlorpheniramine	50/1080	ND	ND	
Triprolidine	6/384	74/6453	1.36 (0.6, 3.11)	12
	3/244	102/6265	0.76 (0.24, 2.36)	9
Diphenhydramine	20/599	6/599	1.56 (1.25, 1.94)	13
	49/595	3199/49 687	1.25 (0.95, 1.64)[c]	8
	1/361	79/6476	0.23 (0.03, 1.63)	12
	4/270	101/6239	0.92 (0.34, 2.47)	9
	80/1461	ND	ND	11
Tripelennamine	6/100	3242/50 182	0.81 (0.37, 1.76)[c]	8
Hydroxyzine	1/74	0/34	1.40 (0.06, 33.51)	14
	5/50	3243/50 232	1.57 (0.68, 3.62)[c]	8
	6/43	2/44	3.07 (0.66, 14.38)	15
	48/828	ND	ND	11
Clemastine	71/1617	ND	ND	11
	39/1230	549/16 967	0.98 (0.72, 1.33)	16
Azatadine	6/127	ND	ND	11
Cyproheptadine	12/285	ND	ND	11

a Number of major/minor fetal malformations in total number of pregnancies exposed to the drug.

b Number of major/minor fetal malformations in total number of pregnancies not exposed to the drug.

c Hospital-standardised relative risk.

ND = no data.

concluded that, as a class, they were safe to use during pregnancy.[28] Based on large numbers, no excess of any specific type of congenital malformations was detected.

2.2.1 Alkylamines

Alkylamines include chlorphenamine (chlorpheniramine), dexchlorpheniramine, brompheniramine and triprolidine.

The Collaborative Perinatal Project found 90 major/minor congenital malformations out of 1070 pregnancies with first trimester exposure to chlorphenamine.[8] A retrospective cohort study and a record linkage study (congenital malformation rate of 3.3%) both looked at exposure to chlorphenamine and failed to demonstrate an increased risk.[11]

Dexchlorpheniramine is the dextrorotatory-isomer of chlorphenamine. In a retrospective record linkage study, 50 malformations out of 1080 exposed pregnancies were observed (congenital malformation rate of 4.6%) and no pattern of defects was detected.[11]

In recent guidelines published on the treatment of allergic rhinitis during pregnancy, chlorphenamine and dexchlorpheniramine are no longer recommended as first-line treatment.[29]

The Collaborative Perinatal Project identified 65 women exposed to brompheniramine in the first trimester of pregnancy. Ten congenital malformations occurred that represented an increased rate as compared with the general population (15% vs 5%).[8] This cohort is grossly underpowered to draw any conclusions. Also, there were no specific clusters of congenital malformations identified and the sample size was very small. The investigators also cautioned that their results did not demonstrate cau-

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sation due to the lack of dose information and the variety of other exposures and underlying diseases in the women studied.[8] In contrast, yet another small cohort could not detect an increased risk for congenital malformations following first-trimester exposure.[9,10] Sixteen women took triprolidine in the first trimester as reported by the Collaborative Perinatal Project. However, the outcomes were not reported in this group.[8] Two other studies did not detect an increased risk for major congenital malformations when brompheniramine was taken in the first trimester.[9,12]

2.2.2 Ethanolamines

Ethanolamines include carbinoxamine, clemastine and diphendydramine. Studies on diphenhydramine provide contradicting results regarding development of congenital malformations. A retrospective study examining diphenhydramine in the first trimester of pregnancy found an increased incidence of cleft palate.[13] In addition, a record linkage study found an increase rate for congenital malformations when looking at 1000 women exposed during the first trimester (80 of 1461 women exposed), although no pattern of defects was found.[11] However, the first study was done retrospectively and, therefore, the participants might have been limited by their recall bias of drug use in their pregnancy and in addition confounding variables, such as other drug exposures, were not used as a matching criteria.[13] However, the Collaborative Perinatal Project and two retrospective cohort studies did not detect any increased risk for congenital malformations when women were exposed in the first trimester.[8,9,12] This combined cohort includes a total of 1226 exposed patients, which is an inadequate sample size to detect a specific malformation such as oral clefts (incidence of 1 in 1000). In addition, Nelson and Forfar,[30] in a retrospective cohort study looking at antihistamine use during the first trimester, could not find any association between major congenital malformations and the drugs. In this study, diphenhydramine was the second most commonly used drug.

In a record linkage study of clemastine, there was no increase in the rate of congenital malformations (71 of 1617 women exposed).[11] The data from the Swedish Medical Birth Registry include 1230 exposures to clemastine with a congenital malformation rate of 3.2%.[16] There are limited data on carbinoxamine use during pregnancy. The Collaborative Perinatal Project reported two exposures during the first trimester; however, pregnancy outcomes were not reported.[8]

2.2.3 Ethylenediamine

The only ethylenediamine is tripelennamine and there are limited data of its exposure in pregnancy. The Collaborative Perinatal Project reported six major/minor congenital malformations of 100 first-trimester exposures.[8]

2.2.4 Piperazines

The only drug in clinical use from piperazines is hydroxyzine. In a record linkage study, the rate of congenital malformations was 5.8%;[11] however,

Table II. Results of teratogenicity studies for antihistamines and decongestants in animals

Drug	Teratogenic correlation with drug	Reference
First-generation antihistamines		
Brompheniramine	Negative	17
Chlorphenamine (chlorpheniramine)	Negative	17
Dexchlorpheniramine	Negative	11
Triprolidine	Negative	18
Diphenhydramine	Positive	19
	Negative	17
Tripelennamine	Negative	18
Hydroxyzine	Positive	20
	Negative	21
Clemastine	Negative	11
Azatadine	Negative	11
Cyproheptadine	Positive	22
	Negative	11
	Negative	23
Second-generation antihistamines		
Cetirizine	Negative	24
Astemizole	Positive	19
	Negative	17
Loratadine	Negative	25
Terfenadine	Negative	26
Oral decongestants		
Phenylephrine	Positive	17
Phenylpropanolamine	Negative	27
Ephedrine	Positive	11
Intranasal decongestants		
Phenylephrine	Positive	17

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Table III. Summary of teratogenicity studies for second-generation antihistamines in humans

Drug	Exposed[a]	Control[b]	Relative risk (95% CI)	Reference
Cetirizine	2/33	2/38	1.15 (0.17, 7.73)	15
	36/917	552/17 280	1.22 (0.89, 1.69)	16
Astemizole	2/114	2/114	1 (0.14, 6.98)	31
Loratadine	61/1796	527/16 401	1.05 (0.83, 1.34)	16
	5/143	6/150	0.93 (0.48, 1.79)	32
	4/175	25/844	0.80 (0.32, 2.00)	33
	11/33	547/1957	1.29 (0.62, 2.68)[c]	34
Terfenadine	51/1031	ND		11
	37/1164	551/17 033	0.98 (0.72, 1.35)	16

a Number of major/minor fetal malformations in total number of pregnancies exposed to the drug.

b Number of major/minor fetal malformations in total number of pregnancies not exposed to the drug.

c Odds ratio as it was a case-control study.

ND = no data.

two early prospective cohort studies and one more recent one were all negative for an association between hydroxyzine exposure during pregnancy and birth defects, although these studies only included 167 exposures.[8,14,15]

2.2.5 Piperidines

There are limited data on piperidines use during pregnancy, although all reported data did not detect an increased rate of congenital malformations for women exposed to these drugs. A record linkage study looking at azatadine and cyproheptadine did not detect an association between these drugs and congenital malformations (6 of 127 exposed for azatadine and 12 of 285 exposed for cyproheptadine).[11] The Collaborative Perinatal Project also reported data on three women exposed to cyproheptadine, although no data on the pregnancy outcome was given.[8]

2.3 Second-Generation Antihistamines

Second-generation antihistamines are mainly lacking the central nervous adverse effects of their earlier counterparts and are, therefore, a first-choice treatment for allergic rhinitis; however, most of them lack large safety studies in pregnancy. A summary of teratogenicity studies for second-generation antihistamines in animals and humans is presented in table II and table III, respectively.

2.3.1 Astemizole

There is one published prospective cohort study on astemizole use during pregnancy. There was no association between first-trimester exposure to the drug and the occurrence of major congenital malformations.[31] However, it has been withdrawn in many countries because of cardiotoxicity.

2.3.2 Azelastine

There are no published studies of exposure during pregnancy.

2.3.3 Cetirizine

Cetirizine is an active metabolite of hydroxyzine. Given the negative teratogenicity findings for hydroxyzine (section 2.2.4), it is unlikely that cetirizine would be a serious concern for use in pregnancy. There is one published prospective cohort study of its use in pregnancy and the investigators did not find a statistically significant difference between exposed and control groups in the rates of major congenital malformations, although the study only included 33 exposed subjects.[15] The data from the Swedish Medical Birth Registry includes 917 exposures to cetirizine with no increased incidence of congenital malformations.[16]

2.3.4 Fexofenadine

Fexofenadine is a metabolite of terfenadine. There are no epidemiological studies in human pregnancy published; however, in animal studies it was found to be negative for teratogenicity at levels up to 47 times the therapeutic levels.[35] In rats with doses three times the human therapeutic levels, there was a decrease in the number of implantations and an increase in post-implantation loss. It was also found

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that there was a decrease in pup weight gain when mothers were administered fexofenadine.[35]

2.3.5 Loratadine

In a Swedish study, the incidence of hypospadias was twice that of the general population for children born to mothers who had taken loratadine (7 of 1796 women exposed to loratadine).[16,36] This has caused an international wave of concern as the drug is very widely used; however, despite its limited statistical power, it might well be a random effect. This rate was not confirmed in two other controlled studies that were both published in 2003, although both studies had small sample sizes. Neither study showed a significant difference in outcomes between the loratadine-exposed group and the controls. Moretti et al.[32] found a rate of 5 congenital malformations of 161 exposures in the exposed group versus 6 of 161 in control group. In the exposed group, there were no cases of hypospadias (there was one case of hypospadias in the non-exposed control group).[32] Diav-Citrin et al.[33] found the rate of major congenital malformations to be 2.3%, 4% and 3% for loratadine, the other antihistamine group and the non-teratogenic control group, respectively. Again, in this study there were no cases of hypospadias in the loratadine-exposed group.[33] The Centers for Disease Control and Prevention recently examined data from the NBDPS (National Birth Defects Prevention Study) and found no increased risk for second- or third-degree hypospadias.[34,37]

2.3.6 Desloratadine

Desloratadine is the principal metabolite of loratadine. At 230-fold the area under the plasma concentration-time curve in humans at the recommended daily oral dose, animal studies were negative for teratogenicity.[38] However, as with loratadine the concerns regarding hypospadias have been aired, but not proven.[27]

2.3.7 Terfenadine

There have been four studies examining the safety of terfenadine in human pregnancy. In none of the four studies did the investigators find an increase in the rate of congenital malformations.[11,16,39,40] Specific data are available on three of the four studies. In the first study, a record linkage study, the rate of malformations was found to be 4.9% (51 of 1034 women exposed).[11] In the second study, a prospective controlled study, no congenital malformations were found, although a lower mean birth rate was seen among those exposed to terfenadine during the first trimester.[40] The data from the Swedish Medical Birth Registry include 917 exposures to terfenadine with a congenital malformation rate of 3.22%.[16] However, like astemizole, it has been withdrawn in many countries because of cardiotoxicity.

2.3.8 Other Antihistamines

Other second-generation antihistamines have not been well studied. There are no human or animal studies that could be located on acrivastine or mizolastine. One published animal study found no association between ebastine and congenital malformations at doses higher than those used in humans.[41]

2.4 Oral Decongestants

Oral decongestants are typically used alone or in conjunction with second-generation antihistamines. They include phenylephrine, phenylpropanolamine and pseudoephedrine. A summary of teratogenicity studies in humans and animals is given in table IV and table II, respectively.

2.4.1 Phenylephrine

There have been contradicting reports published regarding the safety of phenylephrine during pregnancy. The Collaborative Perinatal Project and a case-control study both found an association between the drug and the occurrence of congenital malformations.[42,46] However, a retrospective cohort study could not find any association between exposure to the drug and congenital malformations.[9] In two case-control studies that investigated the association between phenylephrine and cardiac defects, gastroschisis and vascular disruption defects, no association could be confirmed.[43,44]

2.4.2 Phenylpropanolamine

In two early studies, contradicting results were found on the association between phenylpropanolamine and congenital malformations. The Collaborative Perinatal Project found a positive occurrence between the drug and congenital malformations, although a retrospective cohort study did not.[8,9] Two other studies examined the risk of gastroschisis

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Table IV. Summary of teratogenicity studies for oral decongestants in humans

Drug	Exposed[a]	Control[b]	Relative risk (95% CI)	Reference
Phenylephrine	102/1249	3146/49 033	1.23 (1.02, 1.49)[c]	8
	10/390	15/1254	1.70 (1.05, 2.78)	42
	6/301	99/6208	1.25 (0.55, 2.83)	9
	10/298	25/738	0.99 (0.58, 1.69)	43
	0/76	43/2142	0.32 (0.02, 5.13)	44 [d]
	2/416	43/2142	0.27 (0.07, 1.05)	44 [e]
Phenylpropanolamine	71/726	3177/49 556	1.40 (1.11, 1.75)[c]	8
	7/254	98/6255	1.76 (0.83, 3.75)	9
	4/76	74/2142	1.52 (0.57, 4.07)	44 [d]
	19/416	74/2142	1.27 (0.84, 1.91)	44 [e]
	5/110	1/220	2.57 (1.74, 3.8)	45
Pseudoephedrine	1/39	3247/50 243	0.35 (0.05, 2.42)[c]	8
	8/865	72/5972	0.77 (0.37, 1.59)	
	10/665	95/5844	0.93 (0.48, 1.77)	9
	9/76	79/2142	3.25 (1.68, 6.31)	44 [d]
	26/416	79/2142	1.56 (1.1, 2.2)	44 [e]
	9/110	9/220	1.54 (0.95, 2.52)	45
	37/940	ND		11
Ephedrine	17/373	3231/49 909	0.69 (0.43, 1.12)[c]	8

a Number of major/minor fetal malformations in total number of pregnancies exposed to the drug.

b Number of major/minor fetal malformations in total number of pregnancies not exposed to the drug.

c Hospital-standardised relative risk.

d Children born with gastroschisis.

e Children born with vascular disruption.

ND = no data.

associated with phenylpropanolamine use in pregnancy. The results of the studies are contradicting;[44,45] however, a more recent study did not verify gastroschisis suspicions in 206 cases and 798 controls.[47] It must be considered that the viral illness causing the upper respiratory tract infection, and not the drug, may increase the risk for gastroschisis.

2.4.3 Pseudoephedrine

There have been numerous studies that examined the safety of pseudoephedrine during pregnancy and only one found a statistically significant association between the drug and congenital malformations. The Collaborative Perinatal Project,[8] two retrospective cohort studies,[9,12] one case-control study[45] and a record linkage study (malformation rate of 3.9%)[11] were not able to detect an association between the drug and any specific malformation. However, one case-control study found a statistically significant association between pseudoephedrine and gastroschisis and vascular disruption defects.[44] The relative risk for use in the first trimester was found to be 3.2.[44]

2.4.4 Ephedrine

In one published study, 373 women exposed to ephedrine in the first trimester had a congenital malformation rate of 4.6%.[8]

2.5 Intranasal/Ophthalmic Decongestants

The intranasal/ophthalmic decongestants are typically categorised based on their duration of action. For example, phenylephrine is a short-acting agent, naphazoline is an intermediate-acting agent and oxymetazoline is a long-acting agent. A summary of the teratogenicity studies for these drugs in animals and humans can be found in table II and table V, respectively.

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2.5.1 Short-Acting Decongestants

The only short-acting decongestant is phenylephrine and its safety data have already been reviewed in section 2.3.1. These agents have duration of action of up to 4 hours.

2.5.2 Intermediate-Acting Decongestants

Intermediate-acting decongestants include naphazoline and tetryzoline (tetrahydrozoline). These drugs have duration of action of 4–6 hours. There are limited documented data on the use of naphazoline and tetryzoline in pregnancy. The Collaborative Perinatal Project looked at 20 women exposed to naphazoline during pregnancy and one baby was born with a malformation. Three women were exposed to tetryzoline during pregnancy, but the outcomes of these pregnancies were not recorded.[8] A case-control study that looked at the association of these drugs with gastroschisis could not confirm any association.[44]

2.5.3 Long-Acting Decongestants

Long-acting decongestants have duration of action of up to 12 hours. This class includes oxymetazoline and xylometazoline. In two published studies, one retrospective and one case-control, neither drug was found to be significantly associated with congenital malformations.[9,44] The Collaborative Perinatal Project reported two exposures to oxymetazoline and eight exposures to xylometazoline; however, there were no data on the outcomes of the pregnancies.[8] Both drugs are widely used by pregnant women.

2.6 Ophthalmic Antihistamines

Ophthalmic antihistamines include antazoline, levocabastine and pheniramine. There have been no epidemiological studies in human pregnancy done on any of these drugs except for pheniramine. The Collaborative Perinatal Project monitored 831 women who were exposed to pheniramine during the first trimester of pregnancy and did not detect an increase in congenital malformations.[11]

2.7 Inhaled/Intranasal Corticosteroids

The most common corticosteroids used to treat allergic rhinitis are beclometasone, budesonide, dexamethasone, flunisolide, fluticasone propionate, mometasone and triamcinolone.

There are very few population studies on the safety of inhaled or intranasal corticosteroids during pregnancy. In a prospective study looking at the

Table V. Summary of teratogenicity studies for ophthalmic antihistamines and intranasal/ophthalmic decongestants in humans

Drug	Exposed[a]	Control[b]	Relative risk (95% CI)	Reference
Pheniramine	68/831	3180/49 451	1.24 (0.98, 1.56)[c]	8
Phenylephrine	0/76	8/2142	1.61 (0.11, 23.96)	44 [d]
	1/416	8/2142	0.68 (0.11, 4.34)	44 [d]
Naphazoline	1/20	3247/50 262	0.61 (0.09, 4.13)[c]	8
	0/76	2/2142	4.83 (0.38, 61.24)	44 [d]
	0/416	2/2142	1.02 (0.08, 12.87)	44 [e]
Tetryzoline (tetrahydrozoline hydrochloride)	0/76	2/2142	4.83 (0.38, 61.24)	44 [d]
	0/416	2/2142	1.02 (0.08, 12.87)	44 [e]
Oxymetazoline	2/155	103/6354	0.80 (0.2, 3.2)	9
	0/76	18/2142	0.76 (0.05)	44 [d]
	4/416	18/2142	1.12 (0.46, 2.73)	44 [e]
Xylometazoline	5/207	100/6302	1.52 (0.63, 3.7)	9
	0/76	6/2142	2.07 (0.14, 30.14)	44 [d]
	1/416	6/2142	0.88 (0.14, 5.4)	44 [e]

a Number of major/minor fetal malformations in total number of pregnancies exposed to the drug.

b Number of major/minor fetal malformations in total number of pregnancies not exposed to the drug.

c Hospital-standardised relative risk.

d Children born with gastroschisis.

e Children born with vascular disruption.

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safety of beclometasone in 40 women during the first trimester, the incidence of congenital malformations was not significantly different from the baseline rate (1 of 43 live births).[48] In an earlier study examining the safety of beclometasone in first-trimester exposure, there were no congenital defects found that were attributed to the drug.[49] A record linkage study looking at beclometasone exposure during the first trimester could not detect an increased rate for congenital malformations (16 of 395 women exposed).[29]

In 2014 pregnancies exposed to inhaled budesonide, 76 infants in the exposed group had a congenital malformation. The investigators compared this rate of 3.8% to the rate of congenital malformations in the general population (3.5% used in this study) and concluded that it is unlikely that there is any increased risk.[50] Analysis of the data from the manufacturer's postmarketing surveillance did not find clustering of defects.[11] This large sample size and low congenital malformation rate makes it unlikely that the malformations were caused by the drug.

In a randomised, double-blind, placebo-controlled study that looked at the efficacy of fluticasone propionate nasal spray in pregnancy, no effects on the outcomes of the pregnancies were found.[51] The budesonide studies[50] were conducted in pregnant women with asthma where systematic exposure to the inhaled drug was much longer than that encountered in allergic rhinitis.

2.8 Mast Cell Stabilisers

2.8.1 Sodium Cromoglycate (Cromolyn Sodium)

Intranasal sodium cromoglycate (cromolyn sodium) is a mast cell stabiliser used for the prophylaxis of allergic rhinitis. In two studies, one intervention study and one record linkage study, no association between the drug and congenital malformations were found. In the first study, 296 women were treated with sodium cromoglycate in the first trimester (4 babies were born with malformations to 296 women exposed).[52] In the second study, 7 babies were born with malformations to 191 women exposed to sodium cromoglycate.[11] In a third study, there were reassuring data on 151 first-trimester exposures to intranasal and/or inhaled sodium cromoglycate in pregnancy.[53]

2.8.2 Nedocromil

Nedocromil has similar pharmacological action to sodium cromoglycate. In animal studies at doses 800 times the human maintenance dose, nedocromil was not found to be teratogenic.[54]

2.8.3 Lodoxamide

There are no reported controlled teratogenicity studies in human pregnancy.

2.9 Immunotherapy

Allergen immunotherapy is primarily used in patients with chronic symptoms of allergies or hay fever. It differs from pharmacotherapy in that immunotherapy is preventative rather than used to treat symptoms. There have been a number of case reports of women who have used immunotherapy during pregnancy for the treatment of allergic rhinitis, hay fever and dust and pollen asthma without any adverse outcomes reported.[55-59] The Collaborative Perinatal Project did not detect an increase in the rate of major congenital malformations with the use of desensitisation vaccines during pregnancy. However, a statistically significant increase was reported with the use of specific desensitisation vaccines (i.e. house dust extract, poison oak extract and poison ivy extract).[8] Two retrospective cohort studies did not find any association between the use of immunotherapy treatment during pregnancy and major congenital malformations.[60,61] One earlier study found an association between spontaneous

Table VI. Summary of teratogenicity studies for immunotherapy in humans

Exposed[a]	Control[b]	Relative risk (95% CI)	Reference
6/64	3242/50 218	1.32 (0.61, 2.83)[c]	8 [d]
3/14	3242/50 218	4.25 (1.52, 11.87)[c]	8 [e]
3/115	3/119	1.03 (0.21, 5.02)	60
0/105	1/60	1.72[f]	61

a Number of major/minor fetal malformations in total number of pregnancies exposed to the drug.

b Number of major/minor fetal malformations in total number of pregnancies not exposed to the drug.

c Hospital-standardised relative risk.

d Allergy desensitisation vaccine.

e Specific desensitisation vaccine.

f Mantel-Haenszel χ^2 value, p = 0.37.

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abortions and pregnant women exposed to desensitising vaccines and one investigator published a case report of a woman who had an injection of grass pollen vaccine and had a spontaneous abortion.[62,63] The WHO published standards with regards to the use of immunotherapy treatment in pregnancy and it was not contraindicated; however, the WHO did advise to refrain from increasing the dose during pregnancy to prevent an anaphylactic accident.[29] A summary of teratogenicity studies for immunotherapy can be found in table VI.

3. Conclusions

Pharmacological interventions in pregnancy always require a benefit-risk examination of the drug and the underlying condition. Guidelines for the treatment of allergic rhinitis have been published by the ARIA-WHO (Allergic Rhinitis and its Impact on Asthma – in collaboration with WHO).[29] This review exemplifies the fact that there are more than a few treatments available for use during pregnancy with no increased risk for congenital malformations. These treatments are summarised in table VII.

Low-risk therapies could include immunotherapy, intranasal sodium cromoglycate, beclometasone, budesonide and first-generation antihistamines. In a meta-analysis that examined the safety of first-generation antihistamines in pregnancy, 200 000 first-trimester exposures failed to show increased teratogenic risk.[28] Loratadine is the most studied second-generation antihistamine and does not appear to increase the risk of major congenital malformations; however, it has not been as well studied as the earlier antihistamines.

Decongestants have not been conclusively proven to affect the fetal outcome and may be used for short-term relief when no other safer alternatives are available.

Intranasal corticosteroids have not been associated with an increase in congenital malformations in humans. Based on efficacy,[64,65] they can be considered a first-line treatment over oral antihistamines, decongestants and mast cell stabilisers; however, the number of controlled trials in pregnancy is limited. Intranasal corticosteroids are associated with minimal systemic effects in adults and are the most effective therapy for allergic rhinitis. Benefit-risk considerations must, therefore, be done but favour their first-line use during pregnancy.

Table VII. Summary of medications for the management of allergic rhinitis in pregnancy

Evidence of safety	Recommendations
First-line safety	Avoidance of allergens
	Immunotherapy[a]
	Intranasal sodium cromoglycate (cromolyn sodium)
	Intranasal beclometasone, budesonide
	First-generation antihistamines
	chlorphenamine (chlorpheniramine)
	tripelennamine
	hydroxyzine
Second-line safety	Decongestants[b]
	phenylephrine
	oxymetazoline
	Second-generation antihistamines
	loratadine
	astemizole
	cetirizine
Of unproven safety in the first trimester of pregnancy	Fexofenadine

a Only if patient has initiated therapy prior to pregnancy.

b For acute relief only.

Untreated rhinitis during pregnancy may exacerbate existing asthma and, therefore, adversely affect the pregnancy outcome, hence it is important to consider treatment.[66] Untreated rhinitis may also be a problem for the pregnancy by interfering with maternal eating, sleeping and emotional well being. Moreover, it may cause snoring during pregnancy, which has been associated with pregnancy-induced hypertension and intrauterine growth retardation.[67] Although women often choose not to be treated because of unfounded fears of teratogenicity, the option of intervention with drugs should not be discounted given the growing body of evidence on safety. Physicians should follow evidence-based, rather than emotionally based, medicine.

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conflicts of interest that are directly relevant to the content of this review.

References

1. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. J Allergy Clin Immunol 2001; 108 (1 Suppl.): S2-8
2. Mabry RL. Intranasal steroid injection during pregnancy. South Med J 1980; 73 (9): 1176-9
3. Mabry RL. Rhinitis of pregnancy. South Med J 1986; 79 (8): 965-71
4. Mazzotta P, Loebstein R, Koren G. Treating allergic rhinitis in pregnancy: safety considerations. Drug Saf 1999; 20 (4): 361-75
5. Beeley L. Adverse effects of drugs in later pregnancy. Clin Obstet Gynaecol 1981; 8 (2): 275-90
6. Sorri M, Hartikainen-Sorri AL, Karja J. Rhinitis during pregnancy. Rhinology 1980; 18 (2): 83-6
7. Schatz M, Zeiger RS. Diagnosis and management of rhinitis during pregnancy. Allergy Proc 1988; 9 (5): 545-54
8. Heinonen OP, Slone D, Shapiro S. Birth defects and drugs in pregnancy. Littleton (MA): Publishing Sciences Group, 1977
9. Aselton P, Jick H, Milunsky A, et al. First-trimester drug use and congenital disorders. Obstet Gynecol 1985; 65 (4): 451-5
10. Seto A, Einarson T, Koren G. Evaluation of brompheniramine safety in pregnancy. Reprod Toxicol 1993; 7 (4): 393-5
11. Briggs GG, Freeman RK, Yaffe S. Drugs in pregnancy and lactation. 5th ed. Baltimore (MD): Williams and Wilkins, 1998
12. Jick H, Holmes LB, Hunter JR, et al. First-trimester drug use and congenital disorders. JAMA 1981; 246 (4): 343-6
13. Saxen I. Cleft palate and maternal diphenhydramine intake [letter]. Lancet 1974; I (7854): 407-8
14. Erez S, Schifrin BS, Dirim O. Double-blind evaluation of hydroxyzine as an antiemetic in pregancy. J Reprod Med 1971; 7 (1): 35-7
15. Einarson A, Bailey B, Jung G, et al. Prospective controlled study of hydroxyzine and cetirizine in pregnancy. Ann Allergy Asthma Immunol 1997; 78 (2): 183-6
16. Kallen B. Use of antihistamine drugs in early pregnancy and delivery outcome. J Matern Fetal Neonatal Med 2002; 11 (3): 146-52
17. Schardein JL. Chemically induced birth defects. New York: Marcel Dekker Inc, 1993
18. Physicians' Desk Reference. Montvale (NJ): Medical Economics Company, 1989
19. Sciallia AR, Lione A. Pregnancy effects of specific medications used to treat asthma and immunological diseases. In: Schatz M, Zeiger RS, Claman HN, editors. Asthma and immunological diseases in pregnancy and early infancy. New York: Marcel Dekker Inc., 1998
20. King CT, Howell J. Teratogenic effect of buclizine and hydroxizine in the rat and chlorcyclizine in the mouse. Am J Obstet Gynecol 1966; 95 (1): 109-11
21. Steffek AJ, King CT, Wilk AL. Abortive effects and comparative metabolism of chlorcyclizine in various mammalian species. Teratology 1968; 1 (4): 399-406
22. Shepard TH. Catalog of teratogenic agents. Baltimore (MD): The John Hopkins University Press, 1998
23. Pfeifer Y, Sadowsky E, Sulman FG. Prevention of serotonin abortion in pregnant rats by five serotonin antagonists. Obstet Gynecol 1969; 33 (5): 709-14
24. Kamijima M, Sakai KK, et al. Reproductive and developmental toxicity studies of cetirizine in rats and rabbits. Clin Rep 1994; 28: 1877-903
25. Claritin [product information]. Memphis (TN): Schering-Plough Healthcare Products Inc., 2002
26. Gibson JP, Huffmann KW, Newberne JW. Preclinical safety studies with terfenadine. Arzneimittel Forschung 1982; 32 (9a): 1179-84
27. Loratadine, desloratadine and pregnancy: don't use, risk of hypospadias. Prescrire Int 2003; 12 (67): 183
28. Seto A, Einarson T, Koren G. Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis. Am J Perinatol 1997; 14 (3): 119-24
29. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001; 108 (5 Suppl.): S147-334
30. Nelson MM, Forfar JO. Associations between drugs administered during pregnancy and congenital abnormalities of the fetus. BMJ 1971; 1 (5748): 523-7
31. Pastuszak A, Schick B, D'Alimonte D, et al. The safety of astemizole in pregnancy. J Allergy Clin Immunol 1996; 98 (4): 748-50
32. Moretti ME, Caprara D, Coutinho CJ, et al. Fetal safety of loratadine use in the first trimester of pregnancy: a multicenter study. J Allergy Clin Immunol 2003; 111 (3): 479-83
33. Diav-Citrin O, Shechtman S, Aharonovich A, et al. Pregnancy outcome after gestational exposure to loratadine or antihistamines: a prospective controlled cohort study. J Allergy Clin Immunol 2003; 111 (6): 1239-43
34. Centers for Disease Control and Prevention (CDC). Evaluation of an association between loratadine and hypospadias: United States, 1997-2001. MMWR Morb Mortal Wkly Rep 2004; 53 (10): 219-21
35. Allegra [product information]. Kansas City (MO): Aventis Corporation, 2003
36. Kallen B, Olausson PO. Monitoring of maternal drug use and infant congenital malformations: does loratadine cause hypospadias? Int J Risk Saf Med 2001; 14: 115-9
37. Yoon PW, Rasmussen SA, Lynberg MC, et al. The National Birth Defects Prevention Study. Public Health Rep 2001; 116 Suppl. 1: 32-40
38. Clarinex [product information]. Kenilworth (NJ): Schering Corporation, 2002
39. Schick B, Hom M, Librizzi R, et al. Terfenadine (Seldane) exposure in early pregnancy [abstract]. Teratology 1994; 49 (5): 417
40. Loebstein R, Lalkin A, Addis A, et al. Pregnancy outcome after gestational exposure to terfenadine: a multicenter, prospective controlled study. J Allergy Clin Immunol 1999; 104 (5): 953-6
41. Aoki Y, Terada Y. Reproductive and developmental toxicity studies of ebastine (2): teratogenicity study in rats. Yakuri to Chiryo 1994; 22: 1193-215
42. Rothman KJ, Fyler DC, Goldblatt A, et al. Exogenous hormones and other drug exposures of children with congenital heart disease. Am J Epidemiol 1979; 109 (4): 433-9
43. Zierler S, Rothman KJ. Congenital heart disease in relation to maternal use of Bendectin and other drugs in early pregnancy. N Engl J Med 1985; 313 (6): 347-52
44. Werler MM, Mitchell AA, Shapiro S. First trimester maternal medication use in relation to gastroschisis. Teratology 1992; 45 (4): 361-7
45. Torfs CP, Katz EA, Bateson TF, et al. Maternal medications and environmental exposures as risk factors for gastroschisis. Teratology 1996; 54 (2): 84-92
46. Mitchell AA, Schwingl PJ, Rosenberg L, et al. Birth defects in relation to bendectin use in pregnancy: II. Pyloric stenosis. Am J Obstet Gynecol 1983; 147 (7): 737-42
47. Werler MM, Sheehan JE, Mitchell AA. Maternal medication use and risks of gastroschisis and small intestinal atresia. Am J Epidemiol 2002; 155 (1): 26-31

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48. Greenberger PA, Patterson R. Beclomethasone diproprionate for severe asthma during pregnancy. Ann Intern Med 1983; 98 (4): 478-80

49. Brown HM, Storey G. Beclomethasone dipropionate aerosol in long term treatment of perennial and seasonal asthma in children and adults: a report of five and a half years experience in 600 asthmatic patients. Br J Clin Pharmacol 1977; 4: 259S-67S

50. Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. Obstet Gynecol 1999; 93 (3): 392-5

51. Ellegard EK, Hellgren M, Karlsson NG. Fluticasone propionate aqueous nasal spray in pregnancy rhinitis. Clin Otolaryngol 2001; 26 (5): 394-400

52. Wilson J. Disodium cromoglicate use during pregnancy. Acta Ther 1982; 8 (2 Suppl.): 45-51

53. Schatz M, Zeiger RS, Harden K, et al. The safety of asthma and allergy medications during pregnancy. J Allergy Clin Immunol 1997; 100 (3): 301-6

54. Compendium of Pharmaceuticals and Specialties. Ottawa (ON): Canadian Pharmacists Association, 2004

55. Chester SW. Pregnancy and the treatment of hay fever, allergic rhinitis and pollen asthma. Ann Allergy 1950; 8 (6): 772-3

56. Jensen K. Pregnancy and allergic diseases. Acta Allergol 1953; 6 (1): 44-53

57. Maietta AL. The management of the allergic patient during pregnancy. Ann Allergy 1955; 13 (5): 516-22

58. Schaefer G, Silverman F. Pregnancy complicated by asthma. Am J Obstet Gynecol 1961; 82: 182-91

59. Negrini AC, Molinelli G. On desensitizing therapy during pregnancy [in Italian]. Folia Allergol (Roma) 1970; 17 (2): 181-5

60. Metzger WJ, Turner E, Patterson R. The safety of immunotherapy during pregnancy. J Allergy Clin Immunol 1978; 61 (4): 268-72

61. Shaikh WA. A retrospective study on the safety of immunotherapy in pregnancy. Clin Exp Allergy 1993; 23: 857-60

62. Derbes VJ, Soderman WA. Reciprocal influence of bronchial asthma and pregnancy. Am J Med 1946; 1: 367-75

63. Francis N. Abortion after grass pollen injection. J Allergy 1941; 12: 559-63

64. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. BMJ 1998; 317 (7173): 1624-9

65. Yanez A, Rodrigo GJ. Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis. Ann Allergy Asthma Immunol 2002; 89 (5): 479-84

66. Schatz M, Zeiger RS. Asthma and allergy in pregnancy. Clin Perinatol 1997; 24 (2): 407-32

67. Franklin KA, Holmgren PA, Jonsson F, et al. Snoring, pregnancy-induced hypertension, and growth retardation of the fetus. Chest 2000; 117 (1): 137-41

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