Treating Allergic Rhinitis in Pregnancy
Safety Considerations

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Abstract

Allergic rhinitis affects approximately one-third of women of childbearing age. As a result, symptoms ranging from sneezing and itching to severe nasal obstruction may require pharmacotherapy. However, product labels state that medications for allergic rhinitis should be avoided during pregnancy due to lack of fetal safety data, even though the majority of the agents have human data which refute these notions. We present a systematic and critical review of the medical literature on the use of pharmacotherapy for the management of allergic rhinitis during pregnancy. Electronic databases and other literature sources were searched to identify observational controlled studies focusing on the rate of fetal malformations in pregnant women exposed to agents used to treat allergic rhinitis and related diseases compared with controls.

Immunotherapy and intranasal sodium cromoglycate (cromolyn) and beclomethasone would be considered as first-line therapy, both because of their lack of association with congenital abnormalities and their superior efficacy to other agents. First-generation (e.g. chlorpheniramine) and second-generation (e.g. cetirizine) antihistamines have not been incriminated as human teratogens. However, first-generation antihistamines are favoured over their second generation counterparts based on their longevity, leading to more conclusive evidence of

safety. There are no controlled trials with loratadine and fexofenadine in human pregnancy.

Oral, intranasal and ophthalmic decongestants (e.g. pseudoephedrine, phenylephrine and oxymetazoline, respectively) should be considered as second-line therapy, although further studies are needed to clarify their fetal safety. No human reproductive studies have been reported with the ophthalmic antihistamines ketorolac and levocabastine, although preliminary data reported suggest no association between pheniramine and congenital malformations. There are no documented epidemiological studies with intranasal corticosteroids (e.g. budesonide, fluticasone propionate, mometasone) during pregnancy; however, inhaled corticosteroids (e.g. beclomethasone) have not been incriminated as teratogens and are commonly used by pregnant women who have asthma.

In summary, women with allergic rhinitis during pregnancy can be treated with a number of pharmacological agents without concern of untoward effects on their unborn child. Although the choice of agents in part should be based on evidence of fetal safety, issue of efficacy needs to be addressed in order to optimally manage this condition.

The diagnosis of allergic rhinitis refers to episodic symptoms of sneezing, rhinorrhoea, obstruction of nasal passages, conjunctival, nasal and pharyngeal itching and lacrimation all occurring with a temporal relationship to allergen exposure. Although commonly seasonal, this condition can be perennial especially in cases of chronic indoor exposure to allergens such as mite, mould and/or animal dander.

Allergic rhinitis generally affects atopic individuals with symptoms usually appearing before the fourth decade of life. Typically, there is a gradual decrease in the occurrence and severity of symptoms with age. It is estimated that allergic diseases occur in approximately 20 to 30% of women of childbearing age hence making these disorders the most common group of medical conditions that complicate pregnancy.[1,2]

A number of concerns have been raised regarding the coexistence of different allergic conditions with pregnancy. These concerns are as follows.

- Are there any effects of the specific condition on the course and outcome of pregnancy?
- Does pregnancy alter the natural course of the specific illness?
- Which of the different available agents for each condition can be used safely during pregnancy

with respect to both maternal and fetal well-being and safety?

This review will attempt to provide evidence-based answers regarding the effects of allergic rhinitis therapy during pregnancy on both maternal and fetal outcomes. The issue of fetal outcome, with respect to exposure to pharmacological interventions to treat allergic rhinitis, will be addressed based on studies that used the rate of major/minor congenital malformations as the primary outcome measure. Other outcomes, such as spontaneous abortion and long term effects, will not be discussed based on the limited scope of the review and the paucity of data in these areas.

1. Pathophysiology of Allergic Rhinitis

1.1 General Manifestation of Allergic Rhinitis

The nasal mucosal surface fluid contains immunoglobulin (Ig) A which is present preferentially because of its secretory component and IgE which diffuses from plasma cells distributed in proximity to mucosal surfaces. IgE antibodies fix to the mucosal and submucosal mast cells. Specific IgE antibodies are also distributed in circulating basophilic leucocytes. 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 which are capable of producing tissue oedema as well as late phase reactions leading to an influx of eosinophils. The intensity of the clinical response to inhaled allergens is quantitatively related to the antigen dose, levels of specific IgE antibodies as well as basophilic cell mediator releasibility.

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 and this may be related to the generation of histaminase by the human placenta.[3] Despite the theoretical protective effects of these changes on the course of allergic rhinitis, the actual clinical effects of these changes are presently unknown. More clinically relevant are the data demonstrating that pregnancy-related hormonal changes can lead to nasal mucosal congestion. This nasal mucosal congestion is secondary to increased circulating blood volume and increased activity of the nasal mucosal cells resulting in nasal mucosal swelling and increased secretions.[4]

Nasal symptoms may appear to begin during pregnancy: 'vasomotor rhinitis of pregnancy' is an entity 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, pre-existing 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.[5] Other common symptoms related to rhinitis during pregnancy are ear fullness manifested mainly by autophony secondary to eustachian tube congestion.

2. Safety Data for Pharmacological Interventions in Pregnancy

The majority of drugs that are available to treat allergic rhinitis are labelled as being contraindicated in pregnancy, in part because of the lack of data on the safety of these agents in human pregnancy. Although premarketing animal toxicology studies are performed by drug manufacturers, extrapolation to human pregnancy is often difficult. Therefore, it is only by observational studies of either inadvertent exposures in early pregnancy or treatment of life-threatening complications in pregnancy, that drug safety in pregnancy can be established. Such studies determine the overall rate of major congenital malformations compared with the baseline risk of major congenital malformations of 1 to 5% of pregnancies,[6] and the reported defects are reviewed to determine whether or not there is any discernible pattern. Typically, the potential for drug teratogenicity has been reported by various classification systems in different parts of the world. The most common is the US Food and Drug Administration (FDA) 'Use-in-Pregnancy Ratings' that categorises drugs as A, B, C, D and X, based on the level of animal and human evidence to support or refute an association between a drug and congenital anomalies (table I). However, the Teratology Society, an international society of reproductive toxicologists, recently reviewed the FDA classification and concluded that it should be abandoned based on inconsistencies of ratings for a large number of agents.[8] Recommendations were made to replace the rating with narrative statements that summarise and interpret existing teratogenicity data and provide estimates of potential teratogenic risk. Hence, while this review will report the available FDA category for each drug, any summary of teratogenic risk will be made based on statistical interpretation of all available controlled studies regardless of the FDA use-in-pregnancy ratings.

The following sources were searched for relevant articles and reproductive toxicology data: (i) Medline (1966 to April 1998; key words: pregnancy, pregnancy complications, treatment, terato-

Table I. US Food and Drug Administration use-in-pregnancy ratings[7]

Category	Interpretation
A	Controlled studies show no risk. Adequate, well controlled studies in pregnant women have failed to demonstrate risk to the fetus
B	No evidence of risk in humans. Either animal findings show risk, but human findings do not; or, if no adequate human studies have been done, animal findings are negative
C	Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk
D	Positive evidence or risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk
X	Contraindicated in pregnancy. Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk which clearly outweighs any possible benefit to the patient

gens, drug-induced abnormalities, placenta, embryo, fetus, maternal-fetal exchange, toxicology); (ii) bibliographies of retrieved papers; (iii) the Collaborative Perinatal Project;[6]**1** and (iv) a standard toxicology text.[9] Case reports/series were included only in the absence of controlled data. Inclusion criteria were English/French language, pregnancy, pharmacological treatment for allergic rhinitis and associated diseases, and assessment of major/minor congenital malformations after first trimester exposure.

2.1 First Generation Antihistamines

First generation H_1 receptor histamine antagonists (antihistamines) are characterised by their longevity on the market (e.g. diphenhydramine was first introduced on the market in 1946) and their potential for certain adverse effects. A summary of teratogenicity studies for the first generation antihistamines is given in table II.

1 The Collaborative Perinatal Project was a multicentre (US only) observational study to determine the association of a large variety of drugs in a cohort of over 50 000 mother-child pairs during the years 1959 to 1965. It is considered the largest and most documented study of pregnancy outcome following first-trimester exposure to pharmacological agents. Results of the study are reported as follows: cases are the number of major/minor malformations in a total number of pregnancies exposed to the drug; controls are the number of major/minor malformations in the total number of pregnancies not exposed to the drug.

2.1.1 Alkylamines

Drugs in this class include brompheniramine (FDA class C), chlorphenamine (chlorpheniramine) [FDA class B], dexchlorpheniramine and triprolidine (FDA class C).

The Collaborative Perinatal Project identified 10 major/minor congenital out of 65 cases of fetal exposure to brompheniramine during the first trimester, representing a significantly increased rate for congenital anomalies compared with the general population (i.e. 15% in exposed cases *vs* 5% in the general population).[6] No specific clusters of congenital malformations were identified. In contrast, human reproductive data from both prospective and retrospective cohort studies could not detect an increased risk for congenital malformations following first trimester exposure to brompheniramine compared with controls.[11,12]

Chlorphenamine was not found to be significantly associated with congenital malformations in the Collaborative Perinatal Project.[6] Ninety major/minor congenital malformations were identified in over 1000 pregnancies with first trimester exposure to chlorphenamine.[9] Moreover, both a retrospective cohort study[9] and a record linkage study (which indicated a congenital malformation rate of 3.3% following exposure to chlorphenamine)[9] failed to demonstrate an increased risk for congenital malformations with chlorphenamine.

Dexchlorpheniramine is the dextrorotatory-isomer of chlorphenamine. In a retrospective record linkage study, no increase in the rate of major congenital malformations above baseline was ob-

served [i.e. 50 out of 1080 exposed (congenital malformation rate of 4.6%)], and no pattern of defects were detected.[9]

Triprolidine was reported to be taken by 16 women in the first trimester by the Collaborative Perinatal Project.[6] However, the number of babies born with malformations to this group of women was not specified. Two retrospective cohort studies could not detect an increased risk for major con-

genital malformations with triprolidine use in the first trimester.[11,14]

2.1.2 Ethanolamines

The ethanolamines are classified as FDA class B. This group of drugs includes carbinoxamine, clemastine and diphenhydramine.

There is limited data on teratogenicity for both carbinoxamine and clemastine. The Collaborative

Table II. Summary of teratogenicity studies for first generation antihistamines

Animal studies (FDA class)[a]	Human studies	Exposed[b]	Control[c]	RR (95% CI)[d]
Brompheniramine				
Negative[10] (C)	Heinonen et al.[6]	10/65	3238/50 217	2.34 (1.31 to 4.17)
	Aselton et al.[11]	5/172	100/6337	1.84 (0.76 to 4.46)
	Seto et al.[12]	1/34	2/34	0.50 (0.05 to 5.26)
Chlorphenamine (chlorpheniramine)				
Negative[10] (B)	Heinonen et al.[6]	90/1070	3158/49 212	1.2 (0.98 to 1.46)
	Aselton et al.[11]	4/257	101/6252	0.96 (0.36 to 2.6)
Triprolidine				
Negative[13] (C)	Jick et al.[14]	6/384	74/6453	1.36 (0.6 to 3.11)
	Aselton et al.[11]	3/244	102/6265	0.76 (0.24 to 2.36)
Diphenhydramine				
Positive/negative[10,15] (B)	Saxen[16]	20/599	6/599	1.56 (1.25 to 1.94)
	Heinonen et al.[6]	49/595	3199/49 687	1.25 (0.95 to 1.64)
	Jick et al.[14]	1/361	79/6476	0.23 (0.03 to 1.63)
	Aselton et al.[11]	4/270	101/6239	0.92 (0.34 to 2.47)
Tripelennamine				
Negative[13] (B)	Heinonen et al.[6]	6/100	3242/50 182	0.81 (0.37 to 1.76)
Promethazine				
Negative[10] (C)	Nelson & Forfar[17]	22/458	59/911	0.80 (0.56 to 1.16)
	Kullander & Kallen[18]	11/617	95/5753	1.08 (0.58 to 2)
	Rumeau-Rouquette et al.[19]	3/55	178/10 921	3.35 (1.1 to 10.15)
	Heinonen et al.[6]	9/114	3239/50 168	1.17 (0.62 to 2.2)
	Greenberg et al.[20]	45/86	791/1586	1.10 (0.73 to 1.66)
	Mitchell et al.[21]	0/325	6/3153	0.76 (0.05 to 11.04)
	Aselton et al.[11]	0/63	105/6446	0.48 (0.03 to 7.6)
Hydroxyzine				
Positive/negative[22] (C)	Erez et al.[23]	1/74	0/34	1.40 (0.06 to 33.51)
	Heinonen et al.[6]	5/50	3243/50 232	1.57 (0.68 to 3.62)
	Einarson et al.[24]	6/43	2/44	3.07 (0.66 to 14.38)

a   For an explanation of the US Food and Drug Administration (FDA) class see table I.

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

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

d   Heinonen et al.[6] – hospital-standardised relative risk (RR).

CI = confidence interval.

Perinatal Project reported two instances where women were exposed to carbinoxamine during the first trimester of pregnancy; however, the occurrence of major/minor congenital malformations was not reported.[6] The rate of congenital malformations related to clemastine exposure in a record linkage study was not greater than the expected rate in the general population [i.e. 71 out of 1617 exposed (malformation rate of 4.4%)].[9]

A case-control study reported a significant association between fetal exposure to diphenhydramine during the first trimester of pregnancy and the occurrence of cleft palate.[16] In addition, a record linkage study found that the rate of congenital malformations was higher than normal in over 1000 women who were exposed to diphenhydramine during the first trimester of pregnancy [i.e. 80 out of 1461 exposed (malformation rate of 5.5%)], although no pattern of defects was found.[9] Conversely, the Collaborative Perinatal Project and 2 retrospective cohort studies failed to detect an increased risk of congenital malformations in large groups of women who were exposed to diphenhydramine during the first trimester of pregnancy.[6,11,14]

2.1.3 Ethylenediamine

Tripelennamine is the only drug in this class and it is FDA class B. The only published human data on the drug comes from the Collaborative Perinatal Project which reported 6 major/minor congenital malformations out of 100 first trimester exposures to tripelennamine.[6]

2.1.4 Phenothiazines

The phenothiazines are classified as FDA class C. Some drugs of this class have antihistaminic properties and they include methdilazine, promethazine and alimenazine (trimeprazine).

Reproductive toxicology studies on both methdilazine and alimenazine are limited to the Collaborative Perinatal Project which identified 4 and 14 first trimester exposures, respectively.[6] Unfortunately, the number of congenital malformations occurring in each group was not specified.

Safety of promethazine use in pregnancy has been well documented in a number of studies.

These studies include 2 prospective cohort studies,[6,18] 3 case-control studies[17,20,21] and a retrospective cohort study,[11] all of which could not detect an association between promethazine exposure during the first trimester of pregnancy and congenital anomalies. Although a record linkage study [i.e. 61 out of 1197 exposed (malformation rate of 5.1%)][9] and a prospective cohort study[19] both documented an increased risk for congenital malformations, the large number of negative studies previously mentioned would refute the association between congenital malformations and promethazine use in pregnancy.

2.1.5 Piperazines

The piperazines are classified as FDA class C. The single drug representing this class is hydroxyzine. Two prospective cohort studies failed to associate exposure during pregnancy to hydroxyzine with the occurrence of congenital malformations.[6,23] Although the rate of congenital malformations was slightly greater than normal in a record linkage study of hydroxyzine exposure during the first trimester of pregnancy [i.e. 48 malformations out of 828 pregnancies exposed to hydroxyzine (malformation rate of 5.8%)],[9] a recent prospective cohort study confirmed the negative association between hydroxyzine exposure during pregnancy and birth defects.[24]

2.1.6 Piperidines

Piperidines are classified as FDA class B. Drugs of this class include azatadine and cyproheptadine.

There are limited data on the safety of both these drugs in human pregnancy. A record linkage study could not detect an increased rate of congenital malformations in women exposed to azatadine or cyproheptadine during the first trimester of pregnancy [i.e. 6 out of 127 exposed (malformation rate of 4.7%) and 12 out of 285 exposed (malformation rate of 4.2%), respectively].[9] The Collaborative Perinatal Project reported data for 3 women exposed to cyproheptadine during pregnancy, but no data on pregnancy outcome was given.[6]

2.2 Second Generation Antihistamines

Second generation antihistamines have been recently introduced on the market and are best known for the reduced severity of those adverse drug reactions that are prominent with their first generation counterparts. Drugs in this class include astemizole, azelastine, fexofenadine, cetirizine, loratadine and terfenadine. A summary of teratogenicity studies for the second generation antihistamines is given in table III.

2.2.1 Astemizole

Astemizole is classified as FDA class C. One reproductive toxicology study was conducted on astemizole use in human pregnancy. This prospective cohort study did not find an association between astemizole exposure in the first trimester of pregnancy and the occurrence of major congenital malformations.[26]

2.2.2 Azelastine

The FDA class for azelastine is C. No epidemiological studies in human pregnancy have been published with this agent.

2.2.3 Cetirizine

Cetirizine is the active metabolite of hydroxyzine and is classified as FDA class B. One prospective cohort study has investigated the potential teratogenicity of the drug.[24] Although the authors of the study did not find a statistically significant difference between exposed and control groups, the upper 95% confidence interval was high and therefore was not able to detect a large increase (up to 7-fold) in total major congenital malformations. However, given the negative teratogenicity reports of hydroxyzine use in pregnancy, it is not expected that cetirizine poses a serious concern when used in the pregnant patient.

2.2.4 Fexofenadine

Fexofenadine is the active metabolite form of terfenadine and is classified as FDA class C. No epidemiological studies in human pregnancy have been published.

2.2.5 Loratadine

Loratadine is classified as FDA class B. No epidemiological studies in human pregnancy have been reported published with loratadine.

2.2.6 Terfenadine

Terfenadine is classified as FDA class C. Epidemiological studies on terfenadine in human pregnancy are limited to a prospective cohort study[27] and a record linkage study [i.e. 51 out of 1.034 exposed (malformation rate of 4.9%)].[9] The authors in both studies could not detect an increased rate of congenital malformations following exposure to the drug during the first trimester of pregnancy. In addition, a recent preliminary study of terfenadine use in pregnancy also failed to demonstrate an association between the drug and congenital malformations [i.e. 0 babies born to 65 women who were exposed to terfenadine during pregnancy had congenital malformations *vs* 2 babies born to 111 women who were not exposed to terfenadine during pregnancy, p = 0.53] (Lalkin A, personal communication).

2.2.7 Other Agents

To date there are no animal or human studies with acrivastine or mizolastine. There is one pub-

Table III. Summary of teratogenicity studies for second generation antihistamines

Animal studies (FDA class)[a]	Human studies	Exposed[b]	Control[c]	RR (95% CI)
Cetirizine				
Negative[25] (B)	Einarson et al.[24]	2/33	2/38	1.15 (0.17 to 7.73)
Astemizole				
Positive/negative[10,15] (C)	Pastuszak et al.[26]	2/114	2/114	1 (0.14 to 6.98)

a   For an explanation of the US Food and Drug Administration (FDA) class see table I.

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

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

CI = confidence interval; **RR** = relative risk.

lished study on ebastine in animals that found no teratogenicity with doses higher than those used in humans.[28] There are no human studies with ebastine.

2.3 Oral Decongestants

Oral decongestants are used either alone or in combination with second generation antihistamines. They include phenylephrine, phenylpropanolamine and pseudoephedrine. A summary of teratogenicity studies for the oral decongestants is given in table IV.

2.3.1 Phenylephrine

Phenylephrine is classified as FDA class C. Teratogenicity studies regarding phenylephrine use in pregnancy are contradictory. Although the Collaborative Perinatal Project and a case-control study reported a statistically significant association between phenylephrine use during pregnancy and the occurrence of congenital malformations,[21,29] a retrospective cohort study could not detect such an association.[11] Moreover, 2 case-control studies investigating the possible association with cardiac defects, gastroschisis and vascular disruption defects could not confirm such associations.[30,31]

2.3.2 Phenylpropanolamine

Phenylpropanolamine if classified as FDA class C. Documentation of phenylpropanolamine use in human pregnancy includes the Collaborative Perinatal Project[6] and a retrospective cohort study.[11] The former study found a positive association between the drug and the occurrence of congenital malformations, while the latter study failed to detect an association. More recently, 2 case-control

Table IV. Summary of teratogenicity studies for oral decongestants

Animal studies (FDA class)[a]	Human studies	Exposed[b]	Control[c]	RR (95% CI)[d]
Phenylephrine				
Positive[10] (C)	Heinonen et al.[6]	102/1249	3146/49 033	1.23 (1.02 to 1.49)
	Rothman et al.[29]	10/390	15/1254	1.70 (1.05 to 2.78)
	Aselton et al.[11]	6/301	99/6208	1.25 (0.55 to 2.83)
	Zierler et al.[30]	10/298	25/738	0.99 (0.58 to 1.69)
	Werler et al.[31]e	0/76	43/2142	0.32 (0.02 to 5.13)
	Werler et al.[31]f	2/416	43/2142	0.27 (0.07 to 1.05)
Phenylpropanolamine				
Negative[10] (C)	Heinonen et al.[6]	71/726	3177/49 556	1.40 (1.11 to 1.75)
	Aselton et al.[11]	7/254	98/6255	1.76 (0.83 to 3.75)
	Werler et al.[31]e	4/76	74/2142	1.52 (0.57 to 4.07)
	Werler et al.[31]f	19/416	74/2142	1.27 (0.84 to 1.91)
	Torfs et al.[31]	5/110	1/220	2.57 (1.74 to 3.8)
Pseudoephedrine				
None (C)	Heinonen et al.[6]	1/39	3247/50 243	0.35 (0.05 to 2.42)
	Jick et al.[14]	8/865	72/5972	0.77 (0.37 to 1.59)
	Aselton et al.[11]	10/665	95/5844	0.93 (0.48 to 1.77)
	Werler et al.[31]e	9/76	79/2142	3.25 (1.68 to 6.31)
	Werler et al.[31]f	26/416	79/2142	1.56 (1.1 to 2.2)
	Torfs et al.[32]	9/110	9/220	1.54 (0.95 to 2.52)

a   For an explanation of the US Food and Drug Administration (FDA) class see table I.

b   Number of major/minor malformations in total number of pregnancies exposed to drug.

c   Number of major/minor malformations in total number of pregnancies not exposed to drug.

d   Heinonen et al.[6] – hospital-standardised relative risk (RR).

e   In this case-control study, cases were children born with gastroschisis.

f   In this case-control study, cases were children born with vascular disruption.

CI = confidence interval.

studies attempted to identify the association between phenylpropanolamine use in pregnancy and the risk for gastroschisis.[31,32] The results of the studies contradicted each other.

2.3.3 Pseudoephedrine

Pseudoephedrine is classified as FDA class C. A large number of studies have been conducted to determine the effect of pseudoephedrine use in human pregnancy. They include the Collaborative Perinatal Project,[6] 2 retrospective cohort studies,[11,14] 1 case-control study,[32] and a record linkage study that found that 37 babies born to 940 mothers exposed to pseudoephedrine had congenital malformations (malformation rate of 3.9%).[9] None of the aforementioned investigations were able to detect an association between the drug and any specific congenital malformations. However, a recent case-control study found a statistically significant association between pseudoephedrine and the risk for gastroschisis and vascular disruption defects.[31]

2.4 Intranasal/Ophthalmic Decongestants

The intranasal and ophthalmic decongestants are categorised according to their duration of action. They include short-acting agents, e.g. phenylephrine, intermediate-acting agents, e.g. naphazoline and tetryzoline (tetrahydrozoline) and long-acting agents, e.g oxymetazoline and xylometazoline. A summary of teratogenicity studies for the intranasal and ophthalmic decongestants is given in table V.

2.4.1 Short-Acting

The short-acting agents have a duration of action of up to 4 hours. Safety data on phenylephrine in human pregnancy has been already been reviewed in section 2.3.1.

2.4.2 Intermediate-Acting

The intermediate-acting agents have duration of action of 4 to 6 hours. Limited data have been documented on the use of naphazoline (FDA class C) and tetryzoline (FDA class unknown) in human pregnancy. The Collaborative Perinatal Project monitored 20 women who were exposed to naph-

azoline during pregnancy and 1 baby was born with a malformation and 3 women who were exposed to tetryzoline during pregnancy, but the outcome of these pregnancies was not recorded.[6] A case-control study investigating the potential association between naphazoline and tetryzoline and gastroschisis could not confirm such an association.[31]

2.4.3 Long-Acting

Long-acting agents have a duration of action of up to 12 hours. The FDA class of oxymetazoline is C and the FDA class of xylometazoline is unknown. These agents were studied in a retrospective cohort investigation and a case-control study.[11,31] Neither drug was found to be significantly associated with congenital malformations in either study. In addition, the Collaborative Perinatal Project documented 2 exposures to oxymetazoline and 8 exposures to xylometazoline during the first trimester of pregnancy.[6] However, the outcome of the pregnancies was not documented.

2.5 Ophthalmic Antihistamines

The ophthalmic antihistamines are classified as FDA class C. This class includes antazoline, ketorolac, levocabastine and pheniramine. No epidemiological studies of the effect of antazoline in human pregnancy have been performed. Although not an antihistamine, ketorolac is an ocular nonsteroidal anti-inflammatory agent that is indicated for the treatment of seasonal allergic conjunctivitis. No epidemiological studies in human pregnancy have been reported for this agent. Levocabastine in a piperidine antihistamine with H_1 receptor antagonist properties. No epidemiological studies in human pregnancy have been reported for levocabastine. Reproductive toxicology studies on pheniramine are limited to the Collaborative Perinatal Project which monitored 831 women who were exposed to the drug during the first trimester of pregnancy and could not detect a statistical significant increase in congenital malformations.[9]

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

Animal studies (FDA class)[a]	Human studies	Exposed[b]	Control[c]	RR (95% CI)[d]
Pheniramine				
None (C)	Heinonen et al.[6]	68/831	3180/49 451	1.24 (0.98 to 1.56)
Phenylephrine				
Positive[10] (C)	Werler et al.[31]e	0/76	8/2142	1.61 (0.11 to 23.96)
	Werler et al.[31]f	1/416	8/2142	0.68 (0.11 to 4.34)
Naphazoline				
None (C)	Heinonen et al.[6]	1/20	3247/50 262	0.61 (0.09 to 4.13)
	Werler et al.[31]e	0/76	2/2142	4.83 (0.38 to 61.24)
	Werler et al.[31]f	0/416	2/2142	1.02 (0.08 to 12.87)
Tetryzoline (tetrahydrozoline)				
None (?)	Werler et al.[31]e	0/76	2/2142	4.83 (0.38 to 61.24)
	Werler et al.[31]f	0/416	2/2142	1.02 (0.08 to 12.87)
Oxymetazoline				
None (C)	Aselton et al.[11]	2/155	103/6354	0.80 (0.2 to 3.2)
	Werler et al.[31]e	0/76	18/2142	0.76 (0.05 to 11.77)
	Werler et al.[31]f	4/416	18/2142	1.12 (0.46 to 2.73)
Xylometazoline				
None (?)	Aselton et al.[11]	5/207	100/6302	1.52 (0.63 to 3.7)
	Werler et al.[31]e	0/76	6/2142	2.07 (0.14 to 30.14)
	Werler et al.[31]f	1/416	6/2142	0.88 (0.14 to 5.4)

a   For an explanation of the US Food and Drug Administration (FDA) class see table I.
b   Number of major/minor malformations in total number of pregnancies exposed to drug.
c   Number of major/minor malformations in total number of pregnancies not exposed to drug.
d   Heinonen et al.[6] – hospital-standardised relative risk (RR).
e   In this case-control study, cases were children born with gastroschisis.
f   In this case-control study, cases were children born with vascular disruption.
CI = confidence interval; **?** = FDA class unknown.

2.6 Inhalational/Intranasal Corticosteroids

The inhalational and intranasal corticosteroids are classified as FDA class C. The corticosteroids most commonly used to treat allergic rhinitis include beclomethasone, budesonide, dexamethasone, flunisolide, fluticasone propionate, mometasone and triamcinolone.

In general, studies on intranasal corticosteroid use in pregnancy are limited. The Collaborative Perinatal Project reported on 16 women who were exposed to either triamcinolone or dexamethasone during pregnancy, but the outcome of the pregnancies was not stated.[6] A record linkage study could not detect an increased rate for congenital malformations in women exposed to beclomethasone during the first trimester [i.e. 16 babies born to 395 women exposed to beclomethasone during pregnancy were born with malformations (malformation rate of 4.1%)].[9] In addition, prospective and retrospective studies with inhaled beclomethasone[33,34] and one prospective study with an undefined corticosteroid injection[1] failed to reveal any congenital defects attributed to the use of the drugs in the first trimester of pregnancy. There are no epidemiological studies reported with budesonide, flunisolide, fluticasone propionate or mometasone in human pregnancy.

2.7 Mast Cell Stabilisers

Mast cell stabilisers are classified as FDA class B.

2.7.1 Sodium Cromoglycate (Cromolyn)

Sodium cromoglycate (cromolyn) is an intranasal mast cell stabiliser used for the prophylaxis of allergic rhinitis. Although no controlled teratogenicity studies exist with sodium cromoglycate, an intervention study involving less than 296 women treated with sodium cromoglycate in the first trimester of pregnancy did not detect an increased rate for malformations [i.e. 4 babies born to 296 women exposed to beclomethasone during pregnancy were born with malformations (malformation rate of 1.4%)].[35] In addition, a record linkage study failed to demonstrate an increased risk for congenital defects in women exposed to sodium cromoglycate during the first trimester of pregnancy [i.e. 7 babies born to 191 women exposed to beclomethasone during pregnancy were born with malformations (malformation rate of 3.7%)].[9]

2.7.2 Lodoxamide

Lodoxamide is an ocular mast cell stabiliser used primarily to treat seasonal allergic conjunctivitis. There are no reported controlled teratogenicity studies in human pregnancy.

2.8 Immunotherapy

The FDA class of allergen immunotherapy is unknown. Allergen immunotherapy is used primarily in patients with chronic symptoms of allergies or hay fever. One author reported a slight increased risk for spontaneous abortions in women exposed to desensitisation vaccines,[36] while another author reported a spontaneous abortion in a woman given an injection of grass pollen vaccine.[37] Conversely, a number of anecdotal case reports have documented successful use of immunotherapy for allergic rhinitis, hay fever, and dust and pollen asthma without untoward effects on fetal outcome.[38-42] The Collaborative Perinatal Project did not detect an increased risk for congenital malformations with the use of an allergy desensitisation vaccine during pregnancy; however, a statistically significant increase was reported with specific desensitisation vaccines (i.e. house dust extract, poison oak extract, poison ivy extract).[6] More recently, 2 retrospective cohort studies each reported a negative association between immunotherapy during the first trimester of pregnancy and congenital malformations.[43,44] A summary of teratogenicity studies for immunotherapy is presented in table VI.

3. Evaluation of Safety Data for Treatment of Allergic Rhinitis in Pregnancy

3.1 Studies with Positive Association for Congenital Anomalies

A number of studies presented in this review have associated drug use for allergic rhinitis in the first trimester of pregnancy with a negative impact on fetal outcome.

Table VI. Summary of teratogenicity studies for immunotherapy

Animal studies (FDA class)[a]	Human studies	Exposed[b]	Control[c]	RR (95% CI)[d]
None (?)	Heinonen et al.[6]e	6/64	3242/50 218	1.32 (0.61 to 2.83)
	Heinonen et al.[6]f	3/14	3245/50 268	4.25 (1.52 to 11.87)
	Metzger et al.[43]	3/115	3/119	1.03 (0.21 to 5.02)
	Shaikh[44]	0/105	1/60	—g

a   For an explanation of the US Food and Drug Administration (FDA) class see table I.

b   Number of major/minor malformations in total number of pregnancies exposed to drug.

c   Number of major/minor malformations in total number of pregnancies not exposed to drug.

d   Heinonen et al.[6] – hospital-standardised relative risk (RR).

e   Allergy desensitisation vaccine.

f   Specific desensitisation vaccine.

g   Mantel-Haenszel χ^2 = 1.72, p = 0.37.

CI = confidence interval; **?** = FDA class unknown.

In 1977, Heinonen and colleagues[6] reported a statistically significant association between congenital anomalies and brompheniramine therapy. The authors, though, correctly cautioned that their results did not demonstrate causation, given the small numbers of exposed patients, the lack of dosage information reported for each drug and the variety of other exposures and underlying diseases in the women studied.

The Collaborative Perinatal Project did not separate data on major and minor birth defects, and since the rate of minor malformations has been documented to be as high as 10%,[6] the apparent positive findings of this study cannot be taken alone as evidence of the potential teratogenicity of the histamine antagonist in question.

In 1974, Saxen[16] detected an association between diphenhydramine use during pregnancy and the development of oral clefts. However, the study was conducted retrospectively, and therefore the participants may be limited by their recall bias of drug use in their pregnancy. In addition, confounding variables, such as other drug exposures, smoking and alcohol use were not used as matching criteria.

Nelson and Forfar,[17] in a retrospective cohort study, reported on antihistamine use during the first trimester of pregnancy and found no associated increased risk for congenital anomalies. In the antihistamine group, diphenhydramine was the second most commonly used drug. Thus, the results by Saxen are not conclusive and no other findings to support this claim have been found.

In 1976, Rumeau-Rouquette and colleagues[19] determined that promethazine was teratogenic based on their prospective cohort study. However, the cohort of women exposed to the drug in this study was small (i.e. 55 women). Furthermore, all other studies undertaken to investigate the potential teratogenicity of promethazine, most of which involved larger numbers of women, were negative. Hence, in our view promethazine should not be considered a human teratogen.

Decongestants have been targeted as potential teratogens based on their mode of action. It has been hypothesised, by a number of authors, that vasoactive medications may be associated with vascular disruption thereby leading to malformations in the fetus.[45,46] For this reason, a number of case-control studies have been undertaken to investigate this issue. Rothman and colleagues[29] found an association between phenylephrine and congenital cardiac defects. However, the weak association may be attributed to the selective recall of the study participants, primarily since the questionnaires were open-ended with regards to drug use during pregnancy. In addition, the cardiac defects in the children of the phenylephrine-exposed group were heterogeneous in nature, and therefore the association may be due to the underlying disease or other drug exposures during the critical period of formation.

Similar arguments may be used for the case-control studies by Werler et al.[31] and Torfs et al.[32] Moreover, the studies by both Werler et al.[31] and Torfs et al.[32] were conducted without taking into account dose, frequency and duration of timing of drug exposure and other confounders, such as alcohol use and underlying medical conditions. Thus, although the positive findings in these studies may warrant future study, in our view, their findings should be taken as preliminary and not conclusive.

The Michigan Medicaid record linkage study[9] reported a higher rate of malformations in the children of women exposed to a number of agents used to treat allergic rhinitis as compared with the general population (i.e. 1 to 5%). The agents included diphenhydramine (5.5%), hydroxyzine (5.8%) and promethazine (5.1%). The data collected, however, did not take into account the mother's disease, concurrent drug use for medical conditions and other exposures, such as alcohol and tobacco use during pregnancy. Therefore, in our view, the rates reported are insufficient to incriminate these drugs as human teratogens, given the negative controlled studies for each agent.

4. Conclusions

Management of any condition in pregnancy requires care-giver and patient to weigh both the risks and benefits of treatment. Since the thalidomide tragedy, the risks of drug therapy in general during pregnancy have been overestimated. This comprehensive review of the literature has revealed that there are a number of pharmacological therapies available for the treatment of allergic rhinitis in pregnancy that have not been proven to be harmful to the fetus. Therapies available for the management of allergic rhinitis during pregnancy are summarised in table VII.

The first generation antihistamines have not be incriminated as human teratogens in a number of controlled studies. In addition, a recent meta-analysis[47] of 24 studies examining the safety of all antihistamines in pregnancy documented over 200 000 first trimester exposures to various antihistamines. No increased teratogenic risk could be detected and, owing to the large numbers, the confidence intervals were very close to unity [odds ratio = 0.76 (95% confidence interval 0.60 to 0.94)].[47] Moreover, these agents, with the excep-

tion of dexchlorpheniramine, have been available for over 40 years, without evidence of adverse effects on fetal outcome. Therefore, if oral therapy is warranted, the first generation antihistamines should be considered as first choice in the management of allergic rhinitis. However, adverse effects of antihistamines, such as CNS depression, may limit their use.

The second generation histamine antagonists have the disadvantage of being on the market for a shorter period of time, and therefore, the number of teratogenicity studies are limited. Hence, caution is advocated in recommending the use of these agents during pregnancy. However, human studies published to date have been unable to demonstrate teratogenicity with these agents. Therefore, these drugs may be attractive to the pregnant patient who is unable to tolerate the adverse effects of oral first generation antihistamines. The fetal safety of loratadine and fexofenadine have not been established in controlled trials and therefore, their use for allergic rhinitis cannot be advocated unless first-line therapies have been tried and have failed.

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

Recommendation	Therapy	Dosage
First-line therapy	Avoidance of allergens	
	Immunotherapy[a]	
	Intranasal sodium cromoglycate (cromolyn)	1-2 sprays, 2-4 times/day
	Intranasal beclomethasone	2 sprays bid[b]
	First generation antihistamines, e.g.	
	chlorphenamine (chorpheniramine)	4mg q4-6h
	tripelennamine	25-50mg q4-6h
	hydroxyzine	25mg q6-8h
Second-line therapy	Decongestants,[c] e.g.	
	phenylephrine	2-3 sprays/drops q4h
	oxymetazoline	2-3 sprays/drops q12h
	Second generation antihistamines, e.g.	
	astemizole	10mg od
	cetirizine	5-10mg od
Of unproven safety in first trimester of pregnancy	Loratadine	10mg od
	Fexofenadine	60mg bid

a   Only if patient has initiated therapy prior to pregnancy.
b   Recommended to use lowest effective dose.
c   For acute relief only.
bid = twice daily; **od** = once daily; **q4h** = every 4 hours; **q4-6h** = every 4 to 6 hours; **q6-8h** = every 6 to 8 hours; **q12h** = every 12 hours.

Phenothiazines, such as promethazine, may be used without concerns about teratogenicity; however, they may cause (self-limited) extrapyramidal adverse effects in the mother and newborn, especially if used near term. Decongestants (oral, intranasal and ophthalmic) have not been definitively proven to adversely affect fetal outcome and may be used for short term relief of symptoms when no other safer alternatives are available.

The intranasal corticosteroids have not been associated with an increase in congenital malformations in humans. They should be considered as first-line therapy in treating allergic rhinitis based on their superiority to oral antihistamines, decongestants and mast cell stabilisers with respect to efficacy.[48] However, the number of controlled trials in pregnancy are limited and, given that intranasal corticosteroid administration is associated with significant systemic absorption at conventional dosages[49-51] use of the lowest effective dosage is recommended.

Mast cell stabilisers (e.g. sodium cromoglycate) have not proven to be teratogenic and can be considered as excellent first-line choices to treat allergic rhinitis, especially in place of intranasal corticosteroids. Allergen immunotherapy has not proven to be teratogenic and is considered clinically useful in improving symptoms;[52] however, the risk of maternal anaphylactic reactions with immunotherapy should not be ruled out and caution is warranted.[53]

There are suitable pharmacological agents available to manage the pregnant patient with allergic rhinitis. It is especially important to treat this condition given that the disease, if uncontrolled, may exacerbate coexisting asthma and hence adversely affect pregnancy outcome.[54] It is important to note, however, that the best first-line approach to managing allergic rhinitis is avoidance of allergens. Simple modification of the patient's environment (e.g. avoidance of pollen and grass during peak seasons, maintaining a well ventilated household, continuous cleaning of carpets and other areas that collect dust and/or animal dander, etc.) can significantly reduce symptoms.[48] If en-

vironmental changes are ineffective, then the choice of drugs depends on the severity of the symptoms and the benefits and risks of treatment to the mother and fetus. Therefore, any recommendation made should be accompanied by informed consent. Although many women may choose not to be treated based on fears of teratogenicity, the option of intervention with drugs should not be discounted given the overwhelming amount of evidence that contradicts such notions.

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