Authors' objectives
To determine the effects of allergic rhinitis therapy during pregnancy on foetal outcomes.

Searching
The following sources were searched for studies in English or French:

MEDLINE (from 1966 to April 1998) using the keywords 'pregnancy', 'pregnancy complications', 'treatment', 'teratogens', 'drug-induced abnormalities', 'placenta', 'embryo', 'fetus', 'maternal-fetal exchange' and 'toxicology';

the bibliographies of retrieved papers;

the Collaborative Perinatal Project; and

a standard toxicology textbook (see Other Publications of Related Interest no.1).

Study selection
Study designs of evaluations included in the review
Observational controlled studies (including retrospective studies) that compared exposed pregnant women with controls were included, as were record linkage studies. Case reports or series were included only in the absence of controlled data.

Specific interventions included in the review
The following therapies were included:

first generation antihistamines including alkylamines (brompheniramine, chlorpheniramine, triprolidine, and dexchlorpheniramine), ethanolamines (carboxinamine, clemastine, and diphenhydramine), ethylenediamine (tripelenamine), phenothiazines (methdilazine, promethazine, and alimenazine), piperazines (hydroxyzine), and piperidines (azatadine and cyproheptadine);

second generation antihistamines including astemizole, azelastine, cetirizine, fexofenadine, loratadine, terfenadine, acrivastine and mizolastine;

oral decongestants including phenylephrine, phenylpropanolamine, pseudoephedrine;

intra-nasal/ophthalmic decongestants including phenylephrine, naphazoline, tetrayzoline, oxymetazoline, and xylometazoline;

ophthalmic antihistamines including antazoline, ketorolac, levocabastine, and pheniramune; inhalational/intra-nasal corticosteroids including beclomethasone, budesonide, dexamethazone, flunisolide, fluticasone propionate, mometasone, and triamcinolone;

mast cell stabilisers including sodium chromoglycate and lodoxamide; and

immunotherapy.

The dose regimes varied.

Participants included in the review
Pregnant women exposed to agents used to treat allergic rhinitis and associated diseases in the first trimester.
Outcomes assessed in the review
The incidence of major and minor foetal malformations.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Twenty studies were included in the review. It was unclear what the study designs were or what the total number of participants was.

Brompheniramine (3 cohort studies including 271 exposed and 56,588 unexposed plus 1 observational study with 65 exposed): the results were inconsistent. The observational study and 1 cohort study reported an increased rate in malformation in the exposed women compared to the general population, while 2 cohort studies reported no increase.

Chlorpheniramine (2 case control studies with 1,327 exposed and 1 observational study with over 100 exposed): no significant association was detected.

Triprolidine (2 case control with 628 exposed and 12,718 controls): no significant association was detected.

Dexchlorpheniramine (1 retrospective record linkage with 1,080 exposed): no significant association was detected.

Ethanolamines: there was limited data on the teratotoxicity of carbinoxamine and clemastine.

Diphenhydramine (1 case control, 1 record linkage, 2 retrospective cohorts, and 1 observational study): the results were inconsistent. Two studies reported an increased rate of congenital abnormalities associated with exposure while 3 studies reported no increase.

Tripelennamine (one observational study): there were 6 major/minor congenital malformations out of 100 exposed.

Methdilazine and alimenazine: no rates of malformations were reported.

Promethazine (2 prospective, 1 retrospective cohorts, 3 case-control studies, 1 record linkage): the results were inconsistent. Two prospective and 1 retrospective cohorts, and 3 case-control studies reported no association between exposure and malformation, while 1 record linkage (1,197 exposed) and 1 prospective cohort reported increased malformation rates in those exposed.

Hydroxyzine (3 prospective cohort studies, 1 record linkage): 3 prospective cohort studies detected no association.
between exposure and malformation, while 1 record linkage study reported the malformation rates in those exposed to be slightly higher than normal (48 out of 828 exposed).

Azatidine and cyproheptadine (one record linkage with 127 and 285 exposed respectively): there were limited data.

Asterizole (1 prospective cohort study): no association was found.

Cefirizine (1 prospective cohort): no association was found, although the confidence limits were wide.

Terfenadine (1 prospective cohort, 1 record linkage and 1 unpublished): no association was reported.

Phenylephrine (1 observational study, 1 retrospective cohort, 3 case-control studies): the results were inconsistent. One observational study and 1 case-control study reported a significant association, while 1 retrospective cohort and 2 case-control studies reported no association.

Phenylpropanolamine (1 observational, 3 case-control, 1 retrospective cohort): the results were inconsistent. One observational and one case-control study reported a positive association, while a retrospective cohort reported no association. One case-control study reported a positive association between exposure and gastroschisis, while 1 case-control reported no such association.

Pseudoephidrine (1 observational study, 2 retrospective cohorts, 2 case-control and one record linkage): the results were inconsistent. One observational study, 2 retrospective cohort studies, one case-control and one record linkage study reported no association, while a recent case-control reported a significant association between exposure and gastroschisis and vascular disruption.

Naphazoline and tetryzoline: there were limited data.

Oxymetazoline and xylometazoline (1 retrospective cohort and 1 case-control study): no association was detected.

Pheniramine (1 observational study with 831 exposed women): no association was reported.

Sodium chromoglycate: no controlled teratogenicity studies were identified. This section reported results for women exposed to beclomethasone.

Immunotherapy (4 arms of 3 studies with 298 exposed and 100,665 controls): 1 study reported no increased malformation rates with allergy densitisation vaccine but a significant increase with specific desentisisation vaccines. Two retrospective cohort studies and 1 observational study reported no association.

Azelastine, fexofenadine, loratadine, acrivastine and mizolastine, antazoline, ketorolac, levocabastine, budesonide, flunisolide, fluticasone propionate, mometasone, lodoxamide: no epidemiological studies in human pregnancy were identified.

**Authors’ conclusions**

Immunotherapy and intranasal sodium chromoglycate and beclomethasone should be considered as first-line therapy for pregnant women with allergic rhinitis. First- and second-generation antihistamines have not been incriminated as human teratogens. First-generation antihistamines are favoured over second-generation counterparts on the basis of their longevity, leading to more conclusive evidence of safety. Oral, intranasal and ophthalmic decongestants should be considered as second-line therapy, although further studies are needed to clarify their foetal safety. Women with allergic rhinitis during pregnancy can be treated with a number of pharmacological agents without concern of untoward effects on the foetus. The choice of agent in part should be based on evidence of foetal safety. Issues of efficacy need to be addressed in order to optimally manage this condition.

**CRD commentary**

The aim of the review was clearly stated. By limiting the literature search to one database relevant studies may have
been omitted. The following limitations of studies reporting a positive association were mentioned in the discussion: small numbers of exposed patients, lack of dosage information; variety of other exposures and underlying disease; lack of separation of major and minor malformations; retrospective studies with potential for recall bias; and lack of matching for confounding variables such as alcohol use, smoking and other drug exposures.

No details were given of the methods used to select the primary studies or extract the data. Validity was not assessed. The limitations reported for some of the primary studies were restricted to those studies reporting a positive association between exposure and malformations. Heterogeneity was neither assessed statistically nor explored where results differed across the studies.

Without further details of the primary studies, including an assessment of validity, the authors' conclusions cannot be considered to be supported by the evidence presented.

**Implications of the review for practice and research**

**Practice:** The authors consider that the best first-line approach to allergic rhinitis is the avoidance of allergens. If this is ineffective, then the choice of drugs depends on the severity of the symptoms and the benefits and risks of treatment to the mother and foetus. Any recommendations on treatment should be accompanied by informed consent. The authors recommendations on treatment included the following:

- phenothiazines such as promethazine may be used without concerns about teratogenicity;
- decongestants may be used for short-term relief of symptoms when no safer alternatives are available;
- intranasal corticosteroids should be considered first-line therapy in treating allergic rhinitis based on their superiority to antihistamines, but the use of the lowest effective dose is recommended;
- mast cell stabilisers can be considered as excellent first-line choices especially in place of intranasal corticosteroids;
- with allergen immunotherapy, the risk of maternal anaphylactic reactions should not be ruled out and these should be used with caution.

**Research:** The authors did not report any implications for further research.

**Bibliographic details**


**PubMedID**

10230583

**Other publications of related interest**


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Animals; Female; Histamine H1 Antagonists /adverse effects /therapeutic use; Humans; Nasal Decongestants /adverse effects /therapeutic use; Pregnancy; Pregnancy Complications /drug therapy; Rhinitis, Allergic, Perennial /drug therapy; Rhinitis, Allergic, Seasonal /drug therapy

**AccessionNumber**
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.