

Venom immunotherapy in the Hymenoptera-allergic pregnant patient

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Natural or iatrogenic causes of anaphylaxis are significant risk factors in pregnancy. A 3% to 5% risk of sting anaphylaxis in any pregnant woman with insect-sting allergy untreated with venom immunotherapy (VIT) can be calculated. Insect-sting anaphylaxis has allegedly caused severe fetal abnormalities and is a potential cause of fetal loss and severe maternal morbidity and/or mortality. Hymenoptera anaphylaxis is a highly preventable cause of anaphylaxis, but VIT may itself carry a risk potential, with an appropriate 5% reaction during buildup and 1% reaction risk during maintenance VIT. To assess the safety of VIT in pregnancy, we have gathered data from 26 women with 43 pregnancies. All the women were receiving VIT. One woman was stung early in pregnancy with anaphylaxis resulting. Outcome of pregnancy was normal. Thirty-six of the pregnancies ended normally. There were two mild adverse reactions to VIT, neither of which required treatment. One child was born with multiple congenital abnormalities of unknown cause. Since congenital malformations may occur as frequently as one in 40 live births, these data do not suggest a significant increased risk from VIT during pregnancy. (J ALLERGY CLIN IMMUNOL 1990;85:709-12.)

Reduction of both fetal and maternal risk factors in pregnancy are the natural concerns of both the pregnant patient and attending physician. Safe and effective pharmacotherapy and immunotherapy of asthma and allergies during pregnancy have been the subject of several studies.^{1, 2} The pregnant patient with stinging-insect venom hypersensitivity represents a specialized problem because of the difficulty in predicting the risk of a sting during pregnancy. Furthermore, only a small number of pregnant patients stung develop anaphylaxis after a sting.³ An anaphylactic reaction, including a reaction after an insect sting, may be associated with fetal abnormalities and may be responsible for severe morbidity or death of either or both mother and fetus.⁴⁻⁶ Anaphylaxis induced by Hymenoptera venom can be prevented by VIT, which also bears potential risk. Because the major clinical trials of VIT 10 years ago excluded pregnant patients,

Abbreviation used

VIT: Venom immunotherapy

the present study was devised to ascertain the frequency of both insect stings and insect-sting reactions during pregnancy, the effect of VIT on this frequency, and, finally, to evaluate the safety of VIT in pregnant women.

MATERIAL AND METHODS

The Committee on Insects of the American Academy of Allergy and Immunology, Milwaukee, Wis., prepared a 29-item questionnaire that was mailed on two occasions to all members and fellows of the American Academy of Allergy and Immunology. The questionnaire requested the following information about each patient who had received VIT during pregnancy: (1) age, (2) address, race, and presence of allergic respiratory disease or atopic eczema, (3) date and total number of all stings that had caused systemic reactions before pregnancy, (4) stinging insects believed to have caused the reaction, (5) nature of symptoms present during the reaction, (6) date of the first and last reactions, (7) date of pregnancy, (8) insect sting during pregnancy, (9) dates, symptoms, and number of insect stings during pregnancy, (10) descriptions of reactions to immunotherapy during pregnancy and how treated, (11) effect of the reaction on the pregnancy, (12) presence or absence of problems during the pregnancy (outcome of the pregnancy), (13) use of epi-

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TABLE I. Risk of anaphylaxis in pregnancy in patients with known insect-sting allergy

Annual risk of	≤10%
Hymenoptera sting	
Sting anaphylaxis*	
Untreated	Approximately 4%/yr (approximately 40% per sting)
Receiving VIT	0.1% to 0.2%/yr (1% to 2% per sting)
VIT anaphylaxis	
Initial	5%
Maintenance	0.1%

*When subject was re-stung by the incriminated insect.

nephrite during pregnancy, and, finally, (14) whether there were birth defects in the offspring.

Twenty-five member physicians responded, 16 of whom reported 26 women with a history of a systemic reaction to a Hymenoptera sting who had experienced 43 pregnancies while they were receiving VIT. The remaining nine physicians who returned the questionnaire had not administered VIT to any of their Hymenoptera-allergic pregnant patients. Phone calls were made to physicians and patients to clarify the information already received and to obtain follow-up data of pregnancies that had terminated since the questionnaire had been submitted.

RESULTS

Two adverse reactions developed during VIT administered during 43 pregnancies in 26 women with a history of a systemic reaction to Hymenoptera-insect stings. One reaction was merely a large local swelling, and the other adverse reaction was a possible exacerbation of asthma that did not require therapy. This pregnancy terminated with spontaneous delivery of a normal infant at term.

Five of the 26 pregnant patients suffered field stings while they were receiving maintenance VIT, only one sting of which was followed by a mild systemic cutaneous reaction not requiring therapy. These pregnancies also resulted in spontaneous delivery of a normal infant at term.

Five of the 43 pregnancies aborted spontaneously, three during the first trimester, and two during the second trimester. Of the remaining 38 pregnancies ending at term, 36 yielded healthy normal babies, one stillborn, and one baby had multiple congenital abnormalities. This child is still alive.

Thirty-eight of the 43 pregnancies studied were in women who had been receiving maintenance VIT before the pregnancy. The remaining five patients started receiving maintenance doses during the course of the

TABLE II. Frequency of complications in pregnancy

	General population (%)	Study group (%)
1st trimester loss	12-15	3/43 (7)
2nd trimester loss	3-4	2/43 (4.6)
Stillborn	0.5	1/43 (2.3)
Neonatal mortality	0.5	0
Placenta previa	0.3	1/43 (2.3)
Congenital anomalies (cardiovascular)	0.15-0.57	1/43 (2.3)

pregnancy. One of the two second-trimester abortions occurred in one of these five patients. The other four spontaneous abortions occurred in patients who were receiving maintenance VIT. Fifteen of the 26 patients in the study had been receiving VIT with a single venom. The number of venoms administered to each individual did not affect the outcome of the pregnancy.

One of two patients with a second-trimester spontaneous abortion was the child of a diethylstilbestrol-treated mother and had experienced a previous miscarriage before VIT was instituted. The other second-trimester abortion was associated with hemorrhage and a placenta previa. The attending physician reported that the fetus was normal.

DISCUSSION

The decision to use any therapeutic modality is based, in part, on knowledge of its risk/benefit ratio. Outlines of some of the parameters to be considered in arriving at such a decision for patients with insect-sting anaphylaxis are presented in Table I.

It is estimated that insect stings occur in adults with an annual frequency up to 10%.³ Epidemiologic studies indicate that from 0.04% to 4% of the general population have a history of having had a systemic reaction to a Hymenoptera sting during their lifetime.³ Forty percent to 60% of subjects with a positive history of such a systemic reaction and positive skin tests develop systemic reactions on being restung by the incriminated insect.⁷⁻⁹

One study indicated that >30% of the general population have significant levels of antivenom IgE by skin tests or RAST.^{3, 10} The risk for sting anaphylaxis in these asymptomatic patients is uncertain. A survey of postmortem sera derived from persons dying unexpectedly and of unknown cause revealed a surprisingly high prevalence of antivenom IgE.¹¹ This suggests that sting anaphylaxis may be an unrecognized cause of sudden death of clinically healthy

adults.¹² VIT reduces the risk of sting anaphylaxis to between 2% and 5%, and reactions to stings occurring in patients after VIT are usually mild.^{13, 14}

There is a small risk during VIT of developing a systemic reaction severe enough to require treatment with epinephrine. The risk of such a reaction is about 1 in 20 (5%) during the induction phase and <1 in 100 (1%) if maintenance dosage has been achieved.¹³ From the epidemiologic studies described above,³ we extrapolated an estimated chance of being stung at 10% per pregnancy. The estimated chance of anaphylaxis, if stung, at 40% to 60%, and the resultant risk of anaphylaxis in any pregnancy at 4% to 6%. This approximates the risk of a reaction occurring during the induction phase of VIT, but this risk is theoretically offset by the fact that these reactions occur while patients are being observed by a physician. The risk is considerably less if the patient becomes pregnant while she is receiving VIT and is maintained with that VIT throughout that pregnancy. There may be risks attached to the use of certain antihistamines and epinephrine in pregnancy.^{15, 16} Therefore, VIT in pregnancy would be logical if such therapy carried no greater risk to the pregnant patient or fetus.

Serious adverse reactions from immunotherapy for allergic respiratory disease have been reported by Lockey et al.¹⁷ Twenty-four fatalities from inhalant allergen immunotherapy have been analyzed, and it appears that subjects with asthma are at increased risk for adverse reactions.¹⁷ One asthmatic reaction from immunotherapy did occur in our study; however, it was mild and did not require treatment. None of the 24 deaths reported by Lockey et al.¹⁷ involved VIT, although one subject was receiving insect whole body extract, as well as extracts derived from aeroallergens. An editorial commenting on this study concluded that there was approximately one death from immunotherapy per year compared to the 7 to 9 million allergy injections administered each year in the United States.¹⁸

A study of the safety of immunotherapy of allergic respiratory disease during pregnancy revealed that the incidence of abortion, congenital malformations in the neonates, and other problems are no greater than problems for the general population.¹⁹

Earlier reviews of the data on complications of pregnancy in the general population indicated a first trimester, spontaneous abortion rate of approximately 15% unrecognized pregnancies,²⁰ a spontaneous abortion rate of 3% to 4% in the second trimester,^{21, 22} and a fetal death rate at full term of 5/1000 cases (0.5%). We encountered, among our 43 pregnancies, an abortion rate of 7% in the first trimester, 4.6% in the second

trimester, and one stillborn at term (Table II), which is in keeping with data from pregnancies in the general population. The incidence of placenta previa at delivery varies widely but averages approximately one in 250 births.²⁴ Mild to severe congenital fetal anomalies have been reported in widely variable rates, with the frequency of diseases of the heart and great vessels ranging between 1.31 and 5.7/1000 births.^{24, 25} There was one such case in this study.

The frequency of complications to mother and fetus in our study did not appear to differ or demonstrate any apparent increase above that observed in pregnant women not receiving VIT. The information from physicians in our study did not identify other significant drug therapy or risk factors. These data that represent the first assessment of risk of VIT during pregnancy indicate that further study is required.

The safety and efficacy of VIT appear to closely resemble that of inhalant allergen immunotherapy, which is already known to be safe and effective for maintenance therapy during pregnancy. Initiating VIT during pregnancy, especially during the developmentally sensitive first trimester, must be carefully considered in light of the relatively greater risk of allergic venom-sting reactions as compared with reactions to inhaled allergens in subjects with respiratory allergic syndromes.

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