

A retrospective study on the safety of immunotherapy in pregnancy

W. A. SHAIKH

Allergy Clinic, Bombay Hospital Institute of Medical Sciences, Bombay, India

Summary

Eighty-one Indian patients received immunotherapy for allergic diseases during 109 pregnancies. Their allergy clinic records were analysed retrospectively and this revealed an incidence similar to or less than the general population with regard to abortion, perinatal mortality, prematurity, toxemia and congenital malformation. A control group of 60 contemporary Indian patients (82 pregnancies) who refused immunotherapy were also analysed retrospectively and this revealed a higher incidence of abortion, prematurity and toxemia as compared with those treated with immunotherapy. It is concluded that immunotherapy for allergic diseases is safe in pregnancy. Immunotherapy is safe even when it is initiated for the first time in a pregnant patient, an aspect not reported in any study until now.

Clinical and Experimental Allergy, Vol. 23, pp. 857–860. Submitted 30 December 1992; revised 4 May 1993; accepted 12 May 1993.

Introduction

Immunotherapy (IT) for allergic diseases has been used since 1911 [1,2]; yet several physicians are still sceptical about its use in pregnancy. A review of the medical literature revealed few studies on the safety of IT in pregnancy [3–9], based on which standard books on allergy have recommended its continued use in pregnancy [10–14]. No such studies have, however, been carried out on an Asian population.

In India, most physicians and obstetricians do not recommend IT during pregnancy and at least one major allergen manufacturer actively prohibits the use of IT in a pregnant patient through literature accompanying the IT vials [15]. This retrospective study was therefore conceived to determine the safety of IT in pregnant atopic Indian patients, especially since there is a genuine increase in problems during pregnancy in untreated allergic subjects as compared with the normal population [16].

Besides, every study on the subject until now as well as books have recommended that IT should not be initiated for the first time in a pregnant patient, an aspect studied here in a small group of patients. An attempt was also made to determine whether there were any adverse effects on children born to mothers treated with IT.

Materials and methods

Between January 1987 and July 1992, 943 patients suffering from allergic disorders were seen at the allergy clinic. Of these, 738 patients (397 men and 341 women) received IT. Eighty-one women became pregnant during the course of IT, some of them more than once, thus constituting a total of 109 pregnancies. Another group of 60 women (also seen in the allergy clinic during the same period) who had never taken IT in the past and who refused to take IT during their 82 pregnancies were used as a control group. Data on all the above patients were obtained from the detailed records kept in the allergy clinic. Obstetric and paediatric details were obtained from the respective consultants and included in the allergy clinic records. Patients were personally questioned for any additional information required. Despite all precautions and efforts, complete data were not available in every case, especially of children born during this study. Since this is a retrospective study, randomization of patients into the two groups was not possible.

Obstetric terms used in the present study were defined as under [17]:

Abortion: expulsion or extraction from its mother of a foetus or embryo weighing less than 500 g (20 completed weeks of gestation) including spontaneously induced abortion.

Perinatal mortality: number of stillborn babies and

first week neonatal deaths of babies weighing 500 g or more at birth.

Toxaemia of pregnancy: (i) persistent hypertension at and above 140/90 mmHg (ii) oedema or proteinuria or both.

Each mother in this study underwent a detailed history, physical examination, estimation of serum IgE levels (radio-immunoassay), skin-prick test with a battery of 90 common allergens, and spirometry and peak nasal inspiratory flow rates (by Youlten's nasal flow meter). The rationale for IT in the treated group was the presence of atopic symptoms with positive skin-prick tests to aero-allergens which could not be avoided completely [10]. Each patient was prescribed a w/v aqueous extract of a single or a mixture of up to six allergens for IT, starting with a bi-weekly, subcutaneously administered injection of 1:25 000 concentration and building up to a maintenance monthly injection of 1:50 concentration. IT contents were restricted to pollen, moulds, insects, dusts and dust mites. Animal danders, fabrics and foods were not included in IT.

Seventy-four patients (102 pregnancies) in the IT treated group, became pregnant after IT was started. The remaining seven patients (seven pregnancies) were already pregnant (first trimester) when IT was initiated. These seven patients did not inform the physician of their pregnancy; four of them deliberately suppressed information and the other three were unaware of their pregnancy until after IT was started.

Patients in both, the IT and control group, were examined by the same physician who also carried out relevant investigations and formulated the contents of IT. All 141 patients (IT treated and control group) were negative for HIV, toxoplasma and VDRL tests. None of them were smokers, alcoholics or drug addicts. Informed consent was obtained from all patients in the IT group and written refusals to take IT obtained from patients in the control group.

All 24 patients who had abortions were carefully reviewed to exclude other risk factors for abortion [17]; none of them had evidence of long travel, rubella, malaria, thyroid disorders, diabetes mellitus, cervical incompetence or uterine abnormalities. All the abortions were spontaneous (none was a medical termination or criminal abortion) and none was a hydatidiform mole.

Results

The results obtained from this study are tabulated in Tables 1-4.

It must be noted that most patients receiving IT in this study (88%) were being treated with high or moderately high dose therapy during pregnancy [18]. The incidence of

Table 1. Characteristic details of patients treated with immunotherapy and control group

Characteristics	Treated with IT	Control group
Total no. of patients	81	60
No. of pregnancies	109	82
Age (years)		
mean	23	24
range	18-35	21-34
<i>Diagnosis</i>		
Asthma $\pm$ other symptoms	63	46
Asthma	7	5
Rhinitis	11	9
<i>Serum IgE levels (Normal: up to 50 kU/l)</i>		
Lowest	225	221
Highest	1960	1640
Mean	531	526
<i>Immunotherapy (% of patients)</i>		
First dilution—1:25 000 w/v	12	—
Other dilutions	16	—
Highest concentration—1:50 w/v	72	—
<i>Reactions with IT</i>		
Local reactions	70	—
Systemic reactions	3	—

complications in the general population (Table 2) were obtained from available Indian literature [17,19,20]. The sole congenital malformation noted in the control group (Table 2) was a child born mute. During this study, there were 73 episodes of reactions with IT. Seventy of these were small local reactions (erythema and oedema <4 cm diameter at the site of injection) [10]. There were three episodes of systemic reactions in three different patients receiving IT; each episode consisting of acute asthma with generalized urticaria and on each occasion the patient was administered a regular maintenance dose of 1:50 concentration. All three episodes of systemic reactions were treated with adrenaline and antihistamine and were easily reversed. All patients in whom local and systemic reactions were noted, delivered normally. One systemic and five local reactions occurred in patients administered IT for the first time in pregnancy.

All 141 patients in this study were young (below 35 years of age) and the majority (121) were diagnosed to be asthmatics. Serum IgE levels were in the atopic range for all 141 patients.

Complete data on all children born to mothers treated with IT during pregnancy were not available. Of the 109 pregnancies in the IT group, there were four abortions

Table 2. Incidence of complications during pregnancy

Complications	Immunotherapy treated population (109 pregnancies)		Control population Not treated with Immuno. (82 pregnancies)		General population (%)
	No	%	No	%	
Abortion	4	3.67	20	24.4	10–15%
Perinatal death (stillbirth + neonatal death)	0	0	2	1.64	60–109 per 1000 births
Prematurity (< 2500 g)	1	0.9	21	25.6	20–36%
Toxaemia	1	0.9	10	12.2	5–15%
Congenital malformation	0	0	1	1.2	2–5%

Table 3. Status of children of mothers treated with IT

No. of children studied (records available for)	60
Age range	5 months–5 years
<i>Serum IgE levels (Normal–up to 80 kU/l)</i>	
Normal	42
Elevated	18
Range	9 kU/l–1640 kU/l
Probable atopic diseases seen	16/60 26.7%
Asthma ± rhinitis	5
Rhinitis	7
Atopic eczema (± asthma/rhinitis)	2
Urticaria	2

Table 4. Characteristics of seven patients in whom IT was started for the first time in pregnancy

Patients (n)	7
Pregnancies (n)	7
<i>Diagnosis</i>	
Asthma	3
Asthma with rhinitis	4
Complications (abortion, perinatal mortality, prematurity, toxaemia, congenital malformation)	0
Reactions with IT	6
	(Systemic 1, local 5)

and 105 deliveries, out of which data could be retrieved for 60 children (Table 3). Data on the remaining 45 children were missing since these were all from other parts of India (outside Bombay city) and though the mothers themselves came for follow-up, they refused to bring their children for further studies. Since the data on the majority of children are available, the missing data are unlikely to change the outcome of this study.

Discussion

Most allergy books mention that it is safe to continue IT in pregnancy, a surmise based on the few available studies on this subject. Although two early studies reported on the possibility of abortion caused by the use of IT during pregnancy [21,22], later studies found no deleterious effects of IT on the pregnant patient [3–9]. The most

widely quoted study of Metzger *et al.* [9] was probably the first controlled trial. However, most of the patients in the control group of this study (60%) were also part of the IT treated group causing doubts about comparisons. Besides, there were patients in that study who had a history of smoking and ingested alcohol and drugs but these factors were not used in comparing the two groups because of lack of data. In the present study, 81 patients (109 pregnancies) were administered IT during pregnancy and compared with a completely different control group of those patients who were never administered IT (60 patients—82 pregnancies) prior to or during their pregnancy.

The incidence of abortion in the control group was higher than that expected in the general population, an observation which is in line with opinion in literature [13,16]. Also, the incidence of abortion was significantly higher in the control group as compared with the IT treated group ($P \leq 0.05$). The incidence of prematurity and toxemia was also higher in the control group but within the expected incidence for the general population.

Though 18 out of 60 children had elevated IgE levels, only 16 had symptoms suggestive of atopic disease which is in accordance with the incidence of atopic disease in the offspring of one atopic parent [12,23]. Incidentally, only two husbands in the IT group gave any evidence of atopic symptoms on close enquiry.

No study on IT in pregnancy until now has reported on the administration of IT for the first time in pregnancy, yet books reviewed for the present study [10–14] categorically mentioned that IT should not be initiated in pregnancy. The seven patients studied here who were already pregnant when IT was started did not develop any complications and all delivered normally (Table 4). Only one child of these seven had elevated IgE levels but none had any symptoms of atopic disease.

Although it would be entirely justifiable in future to proceed to properly randomized studies of IT in pregnancy, it could be concluded from this study that IT during pregnancy does not increase the incidence of complications even when moderately high to high dose therapy is administered and despite the occurrence of local or systemic reactions. Also, the administration of IT during pregnancy does not make the child more susceptible to atopic disease nor is it likely to cause congenital malformations. These conclusions hold true even if IT is administered for the first time in pregnancy.

Acknowledgements

The author would like to express his gratitude to a large number of general practitioners and to pathology, paediatric and obstetric colleagues in several hospitals all over India who contributed data to this study.

References

- 1 Noon L. Prophylactic inoculation against hay fever. *Lancet* 1952; 1:56.
- 2 Freeman J. Further observations on the treatment of hay fever by hypodermic inoculations of pollen vaccine. *Lancet* 1911; 2:814.
- 3 Derbes VJ, Sodeman WA. Reciprocal influence of bronchial asthma and pregnancy. *Am J Med* 1946; 1:346.
- 4 Schaefer G, Silverman F. Pregnancy complicated by asthma. *Am J Obst Gynaec* 1961; 82:182.
- 5 Chester SW. Pregnancy and the treatment of hay fever, allergic rhinitis and pollen asthma. *Ann Allergy* 1950; 8:772.
- 6 Jensen K. Pregnancy and allergic diseases. *Acta Allergol* 1953; 6:44.
- 7 Maietta AL. The management of the allergic patient during pregnancy. *Ann Allergy* 1955; 13:516.
- 8 Negrini AC, Molinelli G. Alcune osservazioni in tempa di terapia iposensibilizzante in corso di gravidanza. *Folia Allergol* 1970; 17:181.
- 9 Metzger WJ, Turner E, Patterson R. The safety of immunotherapy in pregnancy. *J Allergy Clin Immunol* 1979; 61: 268–272.
- 10 Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW. (Eds.) *Allergy—Principles and Practice*. 3rd Edn. St. Louis: C. V. Mosby, 1988:1093–1155, 1329, 1337.
- 11 Patterson R. (Ed.) *Allergic Diseases—Diagnosis and Management*. 2nd Edn. Philadelphia: J. B. Lippincott Company, 1980: 319–20.
- 12 Mygind N. *Essential Allergy*. 1st Edn. Oxford: Blackwell Scientific Publications, 1986:51.
- 13 Lawlor GJ, Fisher TJ. *Manual of Allergy and Immunology*. 1st Edn. Boston: Little Brown and Company, 1981:146.
- 14 Korenblat PE, Wedner HJ (eds.) *Allergy—Theory and Practice*. 2nd Edn. Philadelphia: W. B. Saunders, 1992:459–470.
- 15 Package insert. Desensol Allergen Extracts (for hyposensitization). Bombay, India: E. Merck (India) Pvt. Ltd.
- 16 Turner ES, Greenberger PA, Patterson R. Management of the pregnant asthmatic patient. *Ann Int Med* 1980; 6: 905–18.
- 17 Dawn CS. *Textbook of Obstetrics*. 12th Edn. Calcutta: Dawn Books, 1992:34, 204, 297, 348, 455, 529.
- 18 Lockey RF, Bukantz SC. (Eds.) *Allergen Immunotherapy*. New York: Marcel Dekker Inc., 1991:191–207.
- 19 Dutta DC. *Textbook of Obstetrics*. 3rd Edn. Calcutta: Central Book Agency, 1992:170, 231, 474, 550, 617, 618.
- 20 Menon MKK, Palaniappan B. (Eds.) *Mudaliar and Menon's Clinical Obstetrics*. 9th Edn. Hyderabad: Orient Longman Ltd, 1990:133, 209, 389, 468.
- 21 Cooke RA. Studies in specific hypersensitiveness. III. On constitutional reactions. *J Immunol* 1992; 7:119.
- 22 Francis N. Abortion after grass pollen injection. *J Allergy* 1941; 12:559.
- 23 Smith JM. Incidence of Atopic disease. *Med Clin North Am* 1974; 58:3.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.