

A prospective study on the safety of sublingual immunotherapy in pregnancy

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Abstract

Background: The aim of this study was to determine the safety of sublingual immunotherapy in pregnancy, which has not yet been reported.

Methods: One hundred and fifty-five patients received sublingual immunotherapy with either house dust mite (*D. farinae*) or a mixture of up to five allergens during 185 pregnancies. Twenty-four patients received sublingual immunotherapy for the first time during pregnancy. Follow-up data were analysed with regard to abortion, perinatal mortality, prematurity, toxemia and congenital malformation. Two control groups did not receive immunotherapy; group A (85 patients) received budesonide 400 µg twice daily and group B (40 patients) received rescue salbutamol inhalation. All three groups were on appropriate avoidance measures.

Results: Six-year follow-up data for the sublingual immunotherapy group revealed an incidence of complications less than that in the general population and a higher incidence of complications in both control groups.

Conclusions: This study concludes that sublingual immunotherapy is safe during pregnancy and is also safe when initiated for the first time in a pregnant patient.

Specific immunotherapy (SIT) was introduced in 1911 (1). The efficacy of SIT has been debated (2), and there is scepticism about its safety during pregnancy. However, literature recommends continuing SIT during pregnancy (3–6). Data available up until now is only for subcutaneous SIT (SCIT). The first study on sublingual SIT (SLIT) was published in 1986 (7), yet there are no studies on the safety of SLIT during pregnancy. The WAO position paper on SLIT is silent on this subject (8).

This prospective study was designed to determine the safety of SLIT in pregnancy when it was initiated prior to pregnancy as also for the first time during pregnancy. Adverse effects, if any, in children born to mothers who took SLIT during pregnancy, were also studied.

Methods

This study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice Guidelines.

A total of 2509 consecutive new patients between September 2004 and August 2009 with nasobronchial allergies were

included (Table 1). Of these, 1229 women were allowed to select their mode of treatment, either SLIT or inhaled corticosteroids (ICS) or rescue medication (salbutamol). Each patient was advised appropriate avoidance measures. Six hundred and eighty women patients accepted SLIT as their treatment. Two hundred and eighty patients became pregnant, some more than once resulting in 326 pregnancies. One hundred and fifty-five pregnant patients were on SLIT, 85 on budesonide dry powder inhaler, 400 µg twice daily (group A), and 40 on salbutamol 200 µg as needed (group B). No patient had ever taken SLIT in the past. Patients having rhinitis were prescribed 10 mg cetirizine when needed.

Each patient's data were meticulously recorded and obstetric and paediatric data obtained from their physicians. Although this was a prospective study, randomization of patients into the three groups was not done because the study was designed to allow patients to select their mode of treatment.

Obstetric terms used were defined as:

- 1 Abortion: termination of pregnancy before the foetus becomes viable.

Table 1 Characteristic details of patients

	Avoidance + SLIT	Control A Avoidance + budesonide	Control B Avoidance + rescue salbutamol
No. of patients (total = 280)	155	85	40
No. of pregnancies (total = 326)	185	96	45
Age (years)			
Mean	29 years 8 months	27 years 8 months	32 years 4 months
Range	19–39 years	21–38 years	20–36 years
Diagnosis (%)			
Asthma	40 (25.80)	22 (25.88)	11 (27.50)
Rhinitis	48 (30.97)	26 (30.59)	12 (30.00)
Asthma + rhinitis	67 (43.23)	37 (43.53)	17 (42.50)
Total serum IgE levels (normal, 0–50 IU/ml)			
Lowest – 445	445	480	502
Highest – 4600	3860	4600	4120
Mean – 980	1020	960	975
No. of patients having elevated IgE levels (%)	155 (100)	85 (100)	40 (100)
SLIT (total – 155)			
Single allergen (HDM)	116	–	–
Two to five allergen mix	39	–	–
Adverse reactions with SLIT			
Local reactions (mild itching in oral cavity, swelling of lips)	11	–	–
Systemic reactions	0	–	–

SLIT, sublingual SIT; HDM, house dust mite.

- 2 Perinatal mortality: including late foetal deaths (stillbirth) and early neonatal deaths.
- 3 Toxaemia of pregnancy: multisystem disorder of unknown aetiology characterized by the development of hypertension to the extent of 140/90 mm Hg or more with oedema and/or proteinuria after 20 weeks in a previous normotensive and nonproteinuric pregnant patient.

Each patient underwent a history, physical examination, total serum IgE levels (ELISA), spirometry and peak nasal inspiratory flow rates (PNIFR) and skin prick tests (SPT) to pollen, moulds, dusts, dust mites, animal dander, fabrics, insects and foods.

The indication for prescribing SLIT was the presence of nasobronchial symptoms with positive SPT to aeroallergens. The SIT group was prescribed a course of standardized SLIT, either house dust mite (HDM) (*Dermatophagoides farinae*) or a mixture of two to five allergens, in increasing frequency and potency. SLIT allergens were grass and tree pollen, insects (mosquito, cockroach and house fly) and HDM. None of the allergens were off-label and the same extract from the same manufacturer was used in all patients. SLIT preparations had 3000 allergenic units (AU)/ml; each SLIT drop contained 150 AU of the allergen and was begun with 150 AU/day, increasing to 750 AU/day, then 750 AU twice weekly as maintenance treatment for 5 years.

Of the 185 pregnancies treated with SLIT, it was initiated for the first time in 24 pregnancies and was continued in 161 pregnancies. Patients were examined, investigated and prescribed SLIT by the same physicians. All 280 patients were negative for HIV, TORCH and VDRL, and none were smokers, alcoholics or drug addicts.

Written, informed consent was obtained from the SLIT group, and written refusals to take SLIT were obtained from control groups. Thirty-three patients, who experienced spontaneous abortion, were reviewed to exclude risk factors for abortion. The incidence of complications (9–14) and atopy (15) in the general population (Table 2) was obtained from the published Indian literature. As this study focused on the safety of SLIT during pregnancy, immunological responses to SLIT were not studied.

Results

The results obtained from this study are tabulated in Tables 1 and 2.

Serum IgE levels were elevated in all 280 patients included in this study, and 194 of them (69%) had asthma.

There were no episodes of systemic reactions, but there were 11 episodes of local (oral) reactions to SLIT, consisting of mild itching in the oral cavity and/or swelling of lips. Patients, in whom local reactions were noted, delivered normally.

Forty-seven (26.70%) of the 176 children born to mothers in the SLIT-treated group, 22 (27.85%) of 79 in control A and 10 (29.4%) of 34 in control B had elevated IgE levels. Forty-two children (24.42%) in the SLIT group, 20 (25.32%) in control A and 8 (23.53%) in control B had symptoms of atopic disease. The 24 patients who were prescribed SLIT for the first time did not develop any complications during pregnancy and had no reactions to SLIT. Six of the 24 children (25%) had elevated IgE levels, and 5 (20.83%) had symptoms of atopic disease. These figures are

Table 2 Incidence of complications during pregnancy

	Avoidance + SLIT (total – 185)		Avoidance + budesonide (total – 96) (group A)		Avoidance + rescue salbutamol (group B)		General population
	No.	%	No.	%	No.	%	
Abortion	8	4.32*	15	16*	10	25**	10–20% of all pregnancies [#]
Perinatal deaths (stillbirth and neonatal deaths)	1	0.54	2	2.08	1	2.22	44/1000 births (4.4%)
Prematurity (<2500 g weight)	5	2.70	4	4.17	6	13.33	31% of all live births
Toxaemia	3	1.62	3	3.13	4	8.88	5–15%
Congenital malformation	0	0	0	0	0	0	2.5–4%

SLIT, sublingual SIT.

* $P \leq 0.05$ (comparing SLIT group with groups A and B).[#] $P \leq 0.05$ (comparing group B with general population).

comparable to the incidence of atopic diseases in the general population (11).

The incidence of abortion in the salbutamol group was higher than in the general population ($P \leq 0.05$) and was higher in both control groups when compared with the SLIT group ($P \leq 0.05$). The incidence of perinatal deaths, prematurity and toxemia of pregnancy was also higher in both control groups as compared to the SLIT group, but within the expected incidence for the general population. These data clearly show that the incidence of complications was the lowest in the SLIT group and indeed lower than that seen in the general population.

Discussion

This is the first ever study on the safety of SLIT during pregnancy.

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Only one earlier study has reported on the safety of SCIT when administered for the first time during pregnancy (6). This study provides evidence that as is the case with SCIT (6), even SLIT is safe when initiated for the first time in pregnancy.

The study concludes that SLIT is safe during pregnancy, even when initiated for the first time in a pregnant patient.

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Conflict of interest

The authors have no potential conflict of interest to declare.