

Immuno therapy In Recurrent Spontaneous Abortion: Randomized and Non-Randomized Trials

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Citation

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Abstract

Objective: The present study was conducted to evaluate the efficacy of immunotherapy with husband's lymphocytes in women with recurrent spontaneous abortion (RSA).

Methods: A total of 205 women with three or more consecutive abortions were screened for known causes of recurrent spontaneous abortion. Only 105 women were registered for immunotherapy after excluding the women who had one or the other known cause of abortion. 73 women were registered for immunotherapy against husband's lymphocytes. 32 women were registered under double blind randomized trial. These women were negative for antipaternal cytotoxic antibodies against their husband's cells.

Success rate of immunotherapy was same in both the groups.

Results: Immunotherapy with husband cells in 73 RSA women was carried out in non-randomized trial. Our results show that the success rate was significantly higher (86%) when compared to other groups of the present study i.e. RSA women who declined to enter the trial (33%), dropouts (50%) and antipaternal cytotoxicity negative RSA women (30%). Antipaternal cytotoxic antibodies (APCA) were taken as the measure of immuno-potential. Our results indicate that APCA can be taken as a good indicator for selecting patients for immunotherapy and also to measure whether the RSA women is adequately immunized or not. We have also seen the effect of husband's cells in double blind randomized trial group (32 RSA women). The success rate was 85%, which is comparable to non-randomized trial group.

Conclusions: Our results indicate the importance of immunotherapy with husband's lymphocytes in RSA women and also show that APCA can be considered as one of the important immuno-potentiating factor.

INTRODUCTION

The first trimester miscarriage is the commonest complication of pregnancy (1) affecting 10-20% of clinically recognized pregnancies (2). Recurrent spontaneous abortion (RSA) can be defined as occurrence of three or more clinically detectable pregnancy lose before 20th weeks of gestation from the last menstrual period or less than 500 grams of foetal body weight (5,6). It occurs approximately 1 in 300 pregnant women (7).

RSA can be classified into primary RSA aborters and secondary RSA aborters. Primary RSA aborters are those

women who have lost all previous pregnancies and no live birth. Secondary RSA aborters are those who have at least one successful pregnancy irrespective of the number of pregnancy loss.

In most women who experience recurrent miscarriage, no cause can be identified. Alloimmune mechanisms that prevent mothers from developing immunological responses essential for the survival of the semiallogeneic pregnancy have been proposed as the cause of fifty percent of all these losses. Embryo rejection in animal models appears to depend upon activated natural killer (NK) cells rather than on antigen specific effector cells. It has been shown in animal

model that granulocyte macrophage colony stimulating factor (GM-CSF) may prevent spontaneous abortion by prevention of NK cells and in humans CD56+ lymphoid cells secrete a novel transforming growth factor, α_2 , which has been shown to be immunosuppressive in nature (8,9,10). Activation of the maternal immune system suppresses NK cells (9,11,12). It has been reported that alloimmunization may modify the maternal immune response therefore immunization have been used to prevent further miscarriages (13,14,15,16,17,18).

However, the reports on immunotherapy with husband's cells are controversial the success rate varies from 10 to 82% (13, 16, 17, 19,20,21). On the basis of animal models of abortion and studies of human organ transplant survival, immunization with paternal white cells was proposed as a treatment for alloimmune-mediated pregnancy loss. In our earlier study we carried out an open non-randomized trial (13) and have shown that the efficacy of immunotherapy is related to immune response to allogenic lymphocytes. We further demonstrated that the measurement of antipaternal cytotoxic antibody titer could serve as a marker for immunopotential.

The purpose of this study was to reconfirm the efficacy of immunization with paternal leukocytes as a treatment for unexplained recurrent spontaneous abortion by using both the models i.e. nonrandomized and double blind randomized trials. For this purpose we enrolled a fresh sample of RSA women and divided this into two groups one with 73 women who underwent immunotherapy with husbands cells and only 32 women agreed to under go double blind randomized trial.

MATERIAL AND METHODS

A total of 205 women with recurrent spontaneous abortion (RSA) were referred to the genetics OPD of Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow from March 1997- 2001.

All underwent the following investigations: (i) karyotype of both the spouses; (ii) serology for toxoplasma; (iii) antiphospholipid antibodies (iv) antinuclear antibodies (v) glucose tolerance test; (vi) hysterosalpingogram; (vii) thyroid function test; and (viii) luteal phase plasma progesterone concentrations (ix) pelvic USG. Those who were negative for the above tests were investigated for antipaternal cytotoxic antibodies (APCA). Only those women who were negative for APCA and for all other known causes for recurrent pregnancy loss were selected for

immunotherapy with allogenic lymphocytes. The details of the protocol approved by the ethical committee of the Institute were explained to all eligible couples and only those who gave written, informed consent were included in the study.

DOUBLE BLIND RANDOMIZED TRIAL

Randomized numbers were generated with computer and double blind randomized trial was carried out where, the patient as well as the treating doctor was not knowing with what he/she was immunizing the RSA women. To keep it blind, blood was collected from both husbands as well as from the RSA wife in all the cases.

APCA ASSAY

The presence of APCA was detected by a cross match between maternal serum and paternal peripheral blood lymphocytes (PBL), using the extended National Institute of Health (NIH) protocol and serum was serially diluted to 1:64. Cross matching was carried out at, 4°C, 22°C and 37°C against total mononuclear cells. (T cells and B cells) A positive result was recorded when = 50% cell death was observed at a serum dilution of 1: 16 or greater.

IMMUNIZATION PROTOCOL

Twenty ml of husband's peripheral blood was collected in preservative free heparin. All procedures were carried out under strict aseptic conditions using plastic disposables and a vertical laminar flow hood. The mononuclear cells were isolated on a Ficoll-Hypaque density gradient. These were washed three times with Roswell Park Memorial Institute (RPMI) 1640 medium and cell concentration was adjusted to 5×10^6 cells/ml. An aliquot of the final preparation was sent for microbiological testing. A total of 5×10^6 cells were injected intradermally, under medical supervision, at three separate sites in the forearm of the women. Immunization was repeated at four-weekly intervals up to a maximum of six times. Each immunization was followed by analysis for APCA at the time of the next immunization. Immunization was stopped when APCA titer of = 1: 16 was achieved. The husband was tested for Rhesus factor (Rh), hepatitis B surface antigen (HbsAg) and human immunodeficiency virus (HIV) antibodies. A history of penicillin allergy was taken from all the recipients, since the medium in which the cells were finally suspended contained penicillin.

STATISTICAL ANALYSIS

χ^2 test was used to compare the outcome in different groups. The SPSS/ PCT statistical package for IBM PC was used to

calculate logistic regression to calculate the logistic regression to consider the effect of serum titers other than 1:16 for statistical validity.

RESULTS

IMMUNOTHERAPY

Out of 105 RSA women with three or more than three abortions only 73 women were registered for non randomized trial and remaining 32 were registered under double blind randomized trial. Development of APCA was taken as immuno-potentiating factor. Once these antibodies developed women were advised to conceive.

NON RANDOMIZED TRIAL

Out of the 73 RSA women who were registered to receive paternal lymphocytes nine (9) were found to be positive for APCA at initial screening hence were excluded for immunotherapy. These were grouped as first group of control (group I). Remaining 64 women were offered immunotherapy to which 15 refused to receive immunotherapy these non-willing women were followed up for their next pregnancy results and were categorized into second group of controls (Group II). 6 women who entered into the immunotherapy trial dropped out during the course of immunization without developing APCA, and were labeled as third group of controls (Group III). Forty-three women went through the entire course of immunization, out of these 43 women. 13 did not develop APCA and were categorized into fourth control group (Group IV). Remaining 30 women who successfully converted from seronegative to seropositive status for APCA, following immunotherapy were labeled as study group i.e. Group V (Table 1).

Figure 1

Table 1. Different groups under non randomized trial

Groups	Number
Total RSA patient without known cause	= 73
I APCA positive at initial screening (Control group- I)	= 9
II Declined to enter the trial (Control group II)	= 15
III Dropped outs (Control group III)	= 6
IV Did not develop APCA following Immunotherapy (Control group IV)	= 13
V Adequately immunized (The study group V)	= 30

The status of APCA following each immunization in-group V women is shown in Table 2. None of the women developed adequate titer of cytotoxic antibodies after first injection of husband's lymphocytes. Whereas 2, 3, 4, 6 and 15 women converted to APCA positive status following 2nd, 3rd, 4th, 5th, and 6th immunization respectively.

Figure 2

Table 2. APCA status after immunization with husband's lymphocytes in the study group (group V)

No. of immunization	No. of recipient	APCA Titers			Total APCA positive	Cumulative APCA positive
		1:16	1:32	1:64		
1	30	-	-	-	-	-
2	30	1	1	-	2	2
3	28	1	-	2	3	5
4	25	1	2	1	4	9
5	21	2	1	3	6	15
6	15	-	-	15	15	30

The pregnancy outcome in different control groups (I – IV) and in study group (group V) is shown in Table 3. It is evident from Table 3 that all the thirty women in the study group (group V) became pregnant in-between 1–6 months following immunotherapy. Twenty-six of them gave birth to full term healthy child (86.6%) while 4 (13.6%) aborted again.

Figure 3

Table 3. Pregnancy outcome group following immunotherapy in non randomized trial

Groups	N*	Confirmed pregnancy	Live births	Subsequent proportion	Success %	P value
Not immunized						
I APCA positive at initial screening (control group I)	9	7	5	2	71%	Group I vs V P>0.05 NS
II Declined to enter the trial (control group II)	15	12	4	8	33%	Group II vs V p<0.001
Immunized						
III Dropped outs (control group III)	6	4	2	2	50%	Group III vs V p<0.001
IV Did not develop APCA following immunotherapy (control group IV)	13	10	3	7	30%	Group IV vs V p<0.001
V Adequately immunized (the study group V)	30	30	26	4	86%	

While group I+III vs group V=P<0.01

* N = Number

** APCA = Antipaternal cytotoxic antibodies

Figure 4

Table 4. Pregnancy out come after immunotherapy in double blind randomized trial group

	Group of RSA women	N	Confirmed pregnancy	Live birth	Subsequent abortion	Success %	P value
I	Women received immunotherapy with their own cells (Autologous cells)	8	3	1	2	33%	Group I vs IV p<0.001
II	Women received immunization with saline	6	2	0	2	00%	Group II vs VI p<0.001
III	Dropped out	4	2	1	1	50%	Group III vs VI P<0.001
IV	Women received immunotherapy with their husband's cells	14	14	12	2	85%	
V	Not developed APCA	19	8	2	6	25%	Group V vs VI p<0.001
VI	Developed APCA (>1:16)	13	13	12	1	92%	

* N = Number

** APCA = Antipaternal cytotoxic antibodies

The difference in the outcome of pregnancy in the successfully immunized group (V) compared to those who were not immunized group (II) was statistically significant (P<0.001). Also in the immunized group, the success rate of pregnancy in women who either dropped out or did not develop required titer of APCA when compared to the group V, the difference of the success of pregnancy out come was significant (P<0.01). Comparison of group I (APCA positive at initial screening) with group V did not reveal any significant difference (P>0.05) thus indicating the importance of immuno-potentiating factors, which have protective role in maintaining the pregnancy.

DOUBLE BLIND RANDOMIZED TRIAL

Thirty-two women were registered under double blind randomized trial. These women were grouped into control group I to IV. In control group I, 8 women who received immunotherapy against their own cells (autologous cells) while in-control group II, 6 women received immunization only with sterile normal saline. There were 4 dropped outs from the double blind randomized trial this was labeled as control group III. Fourteen (14) women received their husband's cells and were grouped as study group i.e. group IV. All the women who received autologous cells, saline and no therapy could not develop APCA. In-group IV who received husbands cells thirteen women developed APCA titer of >1:16 while one women failed to develop adequate APCA titer.

All the thirty-two women were followed up for pregnancy out come. Out of the 14 women who received husband's

cells 12 women gave births to normal healthy children, however, two aborted subsequently. Out of 19 women who did not developed APCA titer of > 1:16 pregnancy was confirmed in 8 women, only 2 (25%) gave births to normal healthy children while 6 (75%) aborted. The women who developed APCA titer >1:16, 13 were pregnant and 12 (92.3%) gave birth to normal healthy babies, however, 1 aborted again. Thus over all success rate of immunotherapy against husband's cells was 85% as compared to autologous (33%), saline (0%), dropped outs (50%) (Table 4). In this study we have not seen any adverse effects of immunotherapy as we have carried out one-year follow up of all the successful pregnancies.

DISCUSSION

Women with recurrent abortion without known cause have been treated with allogenic lymphocytes (^{19, 22, 23}) since last decade. The beneficial effect of immunization with allogenic lymphocytes is attributed to the induction of certain immuno-regulatory factors, which may help in the implantation and foetal growth (^{13, 14, 15, 16, 17, 18}). However, immuno-potiation to prevent habitual abortion remains controversial because of (i) controversial effectiveness of treatment. (ii) Mode of action (iii) selection of patients and (iv) possible side effects (_{24, 25}).

In the present study we registered 105 RSA women, of which 73 were registered for immunotherapy with husband's cells as an open trial and remaining 32 were registered for immunotherapy on the basis of double blind randomized trial. Out of 73, 43 RSA women remained with us for the entire course of immunotherapy. Those who either refused to enter the trial or were positive for APCA or dropped out during the course of immunization formed various control groups. A closer examination of the immunotherapy group revealed that the success rate of pregnancy in the adequately immunized group was 86% in the present study, which is in accord to the other reported studies (^{15, 17, 19, 24}).

The major contribution of the present study is that an effort has been made to compare both non-randomized and double blind randomized trials. Our results revealed that APCA status is an important factor to determine the outcome of pregnancy. In both the groups the success rate is comparable i.e. 86% in non-randomized trial group and 85% in double blind randomized trial group.

It has been reported earlier that psychological factors play an important role in the maintenance of pregnancy. However, we could not find any direct evidence for this in our study.

Women who entered the trial and continued up to 6 immunizations, even if the first few immunizations did not work could be called as a group of “self believers”. However, the direct relationship of APCA titers greater than 1: 16 with the success of pregnancy seen in this study is a point against psychological factors in determining the outcome of pregnancy.

We compared our results with the other published clinical trials using paternal lymphocytes immunotherapy and saline or no treatment placebo trials. Success rate in such studies varied from 0 – 46% where no treatment was given, 29 – 76%, where saline was given and 41 – 72%, where autologous lymphocytes were given, success rate with allogenic lymphocyte immunization varied from 10 – 86%. The variability in the results of the earlier studies could be because of small sample size, heterogeneous control and study groups and use of placebo for providing co-intervention. There are only 6 double blind randomized trial (^{19, 23, 26, 27, 28, 29}) with paternal lymphocytes. We did the meta analysis of these studies and found that percentage of successful pregnancies was (58%) in women under going immunotherapy than in controls where no immunization was given (54%).

Various risks and side effects have been reported to be involved in the immunization like increased risk of twin pregnancies, preterm delivery, growth retardation neonatal thrombocytopenia and certain congenital abnormalities (^{24, 25}).

The exact mechanism, which may play a role in the maintenance of pregnancy, is the participation of suppressor cells (^{26, 30}). It was reported that lymphocyte immunization cause an increase in progesterone induced blocking factor (PIBf) in RSA women, which may play a role in the maintenance of pregnancy by balancing the production of cytokines (²¹). Further it was suggested that paternal lymphocytes immunization is responsible for modulation of immunity in women with unexplained recurrent spontaneous abortion as a result of which there is a shift in the balance for cytokine profiles away from Th1 type reactivity to Th2 type reactivity. This shift of cytokines is essential for the maintenance and continuation of successful pregnancy (³¹). Our study indicates the beneficial effect of immunotherapy in both non-randomized and double blind randomized groups. However, the exact mechanisms, which may be responsible for the success of pregnancy, need to be studied further.

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