Efficacy of Immunotherapy in treatment of Recurrent Abortion

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Summary: **A double blind randomised placebo controlled trial was undertaken to test the efficacy of immunotherapy for the treatment of recurrent spontaneous abortion. The patients were assigned to two groups: those who were immunised with their husband's leucocytes (26); and those who received their own plasma (controls) (26). There were 15 pregnancies in each group. The overall success rate was 76.66% (23/30). The success rate in the treated group was 66.6%, and that in the placebo group was 86.6%. There is no significant difference in the post-therapy outcomes amongst both groups. (χ^2=1.24, p>0.5, NS). We conclude that the value of paternal leucocyte immunisation for the prevention of recurrent spontaneous abortion has not been established.**

Introduction

Immunologic mechanisms have been implicated in a number of heretofore unexplained recurrent spontaneous abortions (R.S.A.). Data from experimental animals suggest that Immunisation with leucocytes could prevent an abortion (Branch, 1992). Immunotherapy using the husband's leucocytes has been proposed as a treatment of Unexplained R.S.A. Uncontrolled claims of success can be discounted (Taylor et al 1981) (Unander et al 1986). The validity of this therapy at present rests on a single randomised controlled trial (Mowbray et al 1985). Recent studies have attempted to reproduce Mowbray's data, but have been unable to confirm the benefit initially reported, due to a much higher rate of success in the control group (HO et al 1991) (Cauchi et al 1991). Efficacy of Immunotherapy in the treatment of R. S. A. using paternal leucocytes can thus be questioned. While Immunisation appears to be safe, the potential risks and benefits are yet not established.

We undertook to answer this question by repeating the trial using the same technique and conditions as used in the first trial at St Mary's Hospital, London. We report here the results of a double-blind randomised placebo controlled trial, using paternal leucocytes as the immunising material.

Material and Methods :

The study was undertaken at the Recurrent Spontaneous Abortion Clinic, Sir H. N. Hospital Medical Research Society, Bombay between June 1990 to November 1994. Patients with three or more consecutive first trimester abortions were included in the study after exclusion of the known causes of recurrent spontaneous abortion.

Table 1 : Selection Criteria for "Immunotherapy"

- Three or more consecutive first trimester confirmed spontaneous abortions.
- Chromosomal, anatomic, microbiological, hormonal or other known causes of Recurrent Spontaneous Abortion excluded as far as possible
- Absence in the serum of anti-nuclear autoantibody and lupus anticoagulant type autoantibody (the later assessed by both anticardiolipin ELISA and by activated partial thromboplastin time (APTT).
- Absence of antipaternal lymphocytotoxic antibodies (APCA).
- Not currently pregnant.

Assessment included a physical examination, hysterosalpingogram and/or hysteroscopy, endocrinological tests including thyroid function tests and a karyotype. Standard coagulation tests, APTT, antinuclear antibody and anticardiolipin antibody were performed, and patients excluded if the results were abnormal. Patients were also excluded if they had antipaternal lymphocytotoxic antibodies. 52 couples were included for the trial. HBsAg, HIV and CMV were tested in both partners to avoid therapy related transmission of the above diseases.

Table II

Immunotherapy Follow-up of R.S.A. Cases (Treated Group)

Sr No	Case No.	Age	Abortions	Dose	Follow up
		34	4	8.88x10⁶	LSCS Female child, 3.4 kg.
2	6	26	2	1.55x10⁷	Aborted at 6 wks
3	8	26	4	2.60x10⁷	LSCS, Female child, 3.0 kg
	10	23	3	4.35x10⁷	FTND, Female child, 3.0 kg
5	16	27	5	2.60x10⁷	FTND, Female child, 2.5 kg
6	23	33	5	17.90x10⁶	Aborted at 8 wks
7	28	33	6	3.00x10⁷	Aborted at 8 wks
8	37	40	5	4.20x10⁶	LSCS Male child, 3.25 kg.
9	34	33	5	9.20x10⁶	FTND, Male Child
10	35	20	1	10.20x10⁶	Preterm Deliv 8 mts Male child
11	37	29	1	9.50x10⁶	FTND, details N.A.
12	43	25	1	3.00x10⁷	Aborted at 6 wks
13	47	26	2	35.00x10⁶	FTND, Male child
14	49	30	3	4.55x10⁶	Aborted at 20 wks ? Cause
15	51	35	5	10.50x10⁶	FTND, Female child

Randomization of Patients :

Patients were allotted to one or the other group using randomization cards. The cards were opened only after collecting 350 ml whole blood from the husband in standard acid/citrate/dextrose donor packs. Neither the treating physician nor the patient knew whether they were injected with paternal cells or her own plasma.

Results :

There were 26 patients in each group. Both groups were equally matched in age, parity & patient characteristics. There were 15 pregnancies each in the treated & placebo group till the time of analysis.

Table III

Immunotherapy Follow-up of R.S.A. Cases (Controls)

Sr No	Case No.	Age	Abortion	Follow up
1	2	27	5	FTND Female child, Oct'97
2	4	35	3	LSCS Female child 2.5 kg
3	7	31	5	LSCS Female child, 2.5kg
4	16	30	7	LSCS Female 2.5 kg Oct'9
5	17	26	4	FTND details N.A.
6	18	29	7	LSCS, Male child, 3.6kg. Feb'9.
7	21	28	4	FTND, Male child Oct'9
8	22	28		FTND Female child, 2.45 kg Feb'9
9	25	33	4	Preterm Deliver 35 wks, Female 2.1 kg
10	29	27	1	FTND, Female child, 3.5 kg. Aug'9
11	32	26	1	Aborted at 9 wks
12	39	30	2	Aborted at 20 wks ?incompetent C.X.
13	45	26	1	FTND, Male child, 2.4 kg
14	50	25	5	LSCS, Male Child, 2.2 kg
15	52	29	3	FTND details N.A.

The overall success rate was 76.66% (23/30) The success rate in the treated group was 66.66% (10/15) and that in the placebo group was 86.66% (13/15). Although our study group is small, there is no significant difference in the post-therapy pregnancy outcome amongst the therapy and control groups (x^2=1.24, P>0.5, Not Significant). No obvious maternal or neonatal side-effects were observed.

Discussion

The Feto-Placental unit is a semi-allograft because of the paternal genetic contribution. However the mechanisms by which the fetus avoids immunologic rejection remains mysterious. It has been suggested that the absence of an essential maternal immunoregulatory response to the genetically foreign fetus is the cause of at least some cases of recurrent miscarriage (Taylor, 1981). Initial attempts to improve maternal immunotolerence were based on the evidence that pretransplant blood transfusions decreased rejection of renal allografts (Redman, 1983). Early proponents of leucocyte immunization felt that normal pregnancy required maternal allogenic recognition to stimulate the formation of Blocking Antibodies necessary for pregnancy maintenance. Although immunization of the female partner with the husband's leucocytes has been the most commonly used regime, third party (donor's) leucocytes, seminal plasma, trophoblast preparations and immunoglobulins have also been used. There is no concensus, however, regarding patient selection, dosage, route or timing of immunization. A major criticism of immunization treatment is that it's mechanism of action is still unknown.

Efficacy of Treatment : (Review of Literature)

Controversy regarding the efficacy of Immunotherapy is far from settled. In uncontrolled series, the success rate ranges from 50-80% (Branch et al 1992). Results from clinical studies (randomised & nonrandomised) using husband's leucocytes as immunizing agent are compared with those from various outcomes within control groups where autologous leucocytes, saline and no treatment were used are outlined in Table IV.

Table IV

Summary of results obtained from clinical trials using Husband's Leucocytes (HL) for Immunisation and various Control Groups including Autologous Leucocytes (AL), Saline, and No Treatment (No Rx)

	Success/Total (%) Pregnancy			
Study	**HL**	**AL**	**Saline**	**No. Rx**
Mowbray et al # 1985	17/22(78)	11/27 (41)	-	-
Reznikoff-Etievant et al 1988	28/33 (85)	13/26 (50)	-	2/5 (40)
Ho et al # 1991	40/49 (82)	33/46 (72)	-	-
Cauchi et al # 1991	13/21 (62)	-	19/25(76)	-
Beer 1988	28/39 (72)	-	-	1/44(36)
Beer et al 1988	100/121(83)	-	-	13/51(25)
Smith et al 1988	27/34 (79)	-	-	2/9(22)
Present Series #	10/15 (66)	13/15 (86)	-	-

: Randomised placebo controlled studies

The No Treatment success rates vary from 0-64%, the Saline results from 29-76% and the autologous leucocytes from 41-80%. This amount of variations among control group's outcome needs to be explained.

Recently a meta-analysis was done under the auspices of the American Society of Reproductive Immunology to determine more definitively whether leucocyte immunization improves the live birth rate in women having recurrent miscarriages. Among the women entered into randomised trials, 68% who received paternal leucocytes delivered a live infant in the next pregnancy, compared with a 61% live birth rate in the controls. The risk ratio

was 1.157. Even the most optimistic interpretation indicates that leucocyte immunization is of marginal clinical benefit.

Risks :

Immunotherapy may not be necessarily innocuous.

Table V
Potential Hazards Associated With Immunotherapy

Risk	Observed
1. Graft vs Host disease :	
(a) Mother	Possible in sick patients receiving blood transfusions. Not yet reported after Immunotherapy.
(b) Baby	Possible, but no proven cases.
2. Abnormal Neonates	No major increase in Congenital Abnormalities Post-natal development normal
3. Anaphylaxis & Serum Sickness	Not seen.
4. Virus Transmission	Risk of transmission of Non-A, Non-B-Hepatitis; HIV; CMV
5. Erythrocyte sensitization	No erythroblastosis fetalis reported.
6. Platelet sentisitization	Possible, but not reported.
7. Enhanced autoimmune disease	Not documented

A potential hazard is the transmission of Non-A, Non-B Hepatitis, HIV, CMV and other Viruses. ABO and other blood group incompatibilities are also potential concerns. Graft v/s Host reactions in immunized women are other possibilities. Physicians should be aware of the potential for severe IUGR in the offspring of immunized women (Menge et al 1985) and other groups have not observed any of the above mentioned complications.

Conclusion :

It is difficult to determine whether immunological factors are responsible for some cases of recurrent miscarriage. No diagnostic tests have been found to be clinically useful. In clinical practice Immunotherapy seems to be of only a marginal value in the treatment of Recurrent Spontaneous Aborters.

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