

Reproductive Biology Section

Matched control study of efficacy of lymphocyte immunotherapy in donor oocyte recipients to support or refute the concept of need for histocompatibility antigen sharing of the couple for benefits

J.H. Check, J.R. Liss, A. Diantonio, M.L. Check, M. Duroseau

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, N.J. (USA)

Summary

Purpose: To determine if lymphocyte immunotherapy (LIT) improves outcome in recalcitrant donor oocyte recipients. If LIT was found to be similarly effective in this group, the theory of shared maternal/paternal histocompatibility antigens would seem less plausible because the donor oocyte introduces another group of histocompatibility antigens.

Methods: Donor oocyte recipients with a history of failure to conceive despite at least two previous ETs using donor oocytes were given the option of having LIT. They were matched with the very next recipient who declined LIT therapy. Lymphocyte immunotherapy using the male partner's lymphocytes was given two weeks before transfer and twice more if pregnant.

Results: Only three controls delivered versus recipients treated with LIT.

Conclusions: The fact that benefit from LIT extended to oocyte recipients challenges the concept that lymphocyte immunotherapy is most beneficial for couples sharing histocompatibility antigens.

Key words: Donor oocytes; Recipients; Immunotherapy; Lymphocytes.

Introduction

A previous study found a 51% live delivery rate in women who had failed to have a live baby after at least two embryo transfers (ETs) following lymphocyte immunotherapy (LIT) versus only 16% for matched controls without immune treatment [1]. A retrospective review also reached the same conclusions [2]. The mechanism of how this treatment helps to improve success following ET, or for that matter, in improving outcome in women with recurrent miscarriages, is not known. One theory is that in some instances the fetus is not sufficiently allogeneic because of sharing of certain critical histocompatibility antigens between male and female partners [3-7]. A sufficient allogeneic stimulus is considered essential to permit a TH1 to TH2 cytokine shift allowing the production of blocking antibodies and/or the production of immunomodulatory proteins that inhibit natural killer cell cytolytic activity [8-11].

Theoretically the transfer of embryos derived from donor oocytes would provide another source of histocompatibility antigens besides paternal ones and might allow the induction of P receptors on gamma/delta T cells. Thus, a priori, the beneficial effect of LIT for patients failing after several IVF-ET attempts may not apply to recalcitrant donor oocyte recipients.

However, the possibility exists that the effectiveness of LIT is not necessarily related to the sharing of histocompatibility antigens and that LIT may be effective even for donor oocyte recipients. Perhaps the problem is not that the embryo/fetus is not sufficiently allogeneic but rather the host is relatively insensitive to an allogeneic stimulus as far as inducing P receptors on gamma/delta T cells. The theory continues that the white cell is far more immunogenic than the fetal semi-allograft and can induce de novo the required receptors for P.

The study presented here evaluated the efficacy of LIT for donor oocyte recipients failing to conceive after several ETs.

Materials and Methods

Donor oocyte recipients who failed to have a successful pregnancy following at least two ETs (either fresh or frozen) were offered the option of having LIT performed prior to the next ET. Whenever a recipient decided to have LIT, they were matched to the very next recipient having an ET who did not have LIT performed. Frozen ET was only included if the woman previously failed to have a successful outcome following a fresh ET.

Matching was based on the age of recipient within two years of each other, the same number of failed ETs in recipients, and the same type of transfer (fresh or frozen).

Lymphocytes were taken from the male partners (no donors). To prepare the lymphocytes for immunization, 100 ml of whole blood was obtained from the male partner and the plasma and erythrocytes were removed. The remainder was resuspended

with an equal volume of sterile saline. The cells were then layered over Isoprep and centrifuged. The mononuclear cell layer was then aspirated and washed three to five times with sterile saline with a final slow spin to remove platelets and then resuspended with 0.6 ml of sterile saline. The lymphocyte suspension was then aspirated into a tuberculin syringe. The patients then received three to four intradermal injections from the 0.6 ml suspension.

Intradermal injections were given approximately two weeks before ET – usually day 1-8 of the menstrual cycle. If pregnancy occurred LIT was repeated two more times: after the third doubling of the serum beta human chorionic gonadotropin (hCG) level and six weeks from conception.

Results

Ten recipients received LIT and ten did not. The outcomes of three fresh and seven frozen ET pairs were compared (Table 1). The median number of previously failed transfers was three.

Table 1. — *Effect of LIT on Pregnancy Outcome in Recalcitrant Donor-Oocyte Recipients.*

Treatment	Pregnancy outcome			
	Ectopic	Clinical	Live delivery	Miscarriage
LIT	0	9	9	0
Controls	1	5	3	2

There was one ectopic pregnancy in a woman who did not receive LIT. Clinical pregnancies (ultrasound evidence of intrauterine pregnancy) occurred in nine of ten (90%) pretreated with LIT vs five of ten (50%) of the controls.

There were no miscarriages (0%) in women treated with LIT vs two of five (40%) in controls. The live delivery rate was 90% for women treated with LIT vs 30% for controls ($p = .02$, Fisher's exact test).

Discussion

Unfortunately there were only ten women who received LIT related to the usual success rate with donor oocytes and the preconceived bias that LIT would not benefit a donor egg recipient because of exposure to two allogeneic stimuli. Also, the study was limited in numbers by the U.S. Food and Drug Administration's decision precluding further use of this procedure without a new drug application approval which has basically stopped the use of this technique in the United States.

Despite the small number, the results were consistent with the outcome of the aforementioned matched controlled study and retrospective studies [1, 2].

Whether LIT is beneficial or not is highly controversial. Those who share the opinion that LIT does improve pregnancy outcome (whether women are treated for recurrent miscarriage or failure to have a successful outcome following ET) generally think that the problem is most likely related to the fetus being an inadequate allogeneic stimulus [3-7].

The trend for improved outcome using donated oocytes following LIT in refractory cases has to make one consider that some women may have problems with inadequate immunological response to a normal allogeneic stimulus but may respond to a more potent allogeneic stimulus, e.g., leukocytes from another person. Alternatively, some product from the lymphocyte may enhance the turn off of a gene that produces an inhibitor to P receptor expression. Actually in contrast to the studies suggesting that maternal/paternal sharing of HLA-DQ alpha alleles results in increased risk of fetal loss, our own study failed to demonstrate any disadvantage by sharing this antigen [14].

Hopefully, this small but provocative study will stimulate the interest of a group outside the United States to continue investigations of the efficacy of LIT for patients having problems having a live baby with or without IVF-ET. It is also hoped that these data may stimulate some researchers to evaluate the possibility that one cause of reduced fecundity potential may be a reduced capacity of some women's immune system to respond to a normal allogeneic stimulus.

It should be noted that we share the opinion of other authors that there are no proven tests, e.g., measuring natural killer cell levels, that determine which women would benefit from LIT [12, 13]. We offered LIT to women in the past strictly related to a history of recurrent miscarriage or those with recurrent failures to successfully conceive despite IVF-ET [1, 2, 15].

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Address reprint requests to:
J.H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)