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Lymphocyte Immunotherapy is Not Necessary for Primary Unexplained Abortions

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Review

Human conceptus is a semi-allograft and hence antigenically foreign to the mother, the process of implantation may include mechanisms preventing allograft rejection, once the immunological tolerance is imbalanced, pathological pregnancy, such as spontaneous abortion would occur [1].

Recurrent Pregnancy Loss (RPL) is a disease, defined by two or more failed pregnancies, affecting about 5% pregnant women. RPL can be classified into primary RPL and secondary RPL [2]. Primary RPL aborters are those who have lost all previous pregnancies and have no live birth. Secondary RPL aborters are those who have at least one successful pregnancy, irrespective of the number of pregnancy losses. In 50% to 75% of couples with recurrent pregnancy losses, the etiology is Unknown (URPL), although genetic/chromosomal causes, hormonal abnormalities, metabolic abnormalities, uterine abnormalities, anti-phospholipid syndrome, thrombophilias, male factor have been implicated. URPL is considered to be a model of immunological rejection of the fetus by the mother [3-5].

In 1981, Lymphocyte Immunotherapy (LIT) was performed to treat four URPL patients for the first time, based on the "tolerance" of human kidney allografts, three delivered normal babies and one delivered a premature baby [6]. Since then, LIT have been widely used in patients for alloimmune type RPL, within and outside controlled trials. It attributes to the production of Anti-paternal Cytotoxic Antibodies (APCAs) in women with RPL. Subsequently, many studies confirm the association between recurrent abortions and parent similarity of Human Leukocyte Antigens (HLA) which induces hyporesponsiveness and inhibits production of blocker antibodies as immunological regulators to maintain the pregnancy. Anti-paternal Cytotoxic Antibodies (APCAs), Anti-idiopathic Antibodies (Ab2), and Mixed Lymphocyte Reaction Blocking Antibodies (MLR-Bf) are considered as a part of regulators that cover paternal HLA molecules in the surface of fetuses and make a barrier for attacking the maternal T cells and NK cells [7]. Production of APCA, Ab2, and MLR-Bf antibodies, inhibition of T lymphocytes by reducing the maternal IL-2 receptors, shifting of the Th1 to Th2 immune response [8,9] decreasing NK cell function and enhancing the percentage of $CD4+CD2^{5\ bright}$ regulatory T cells might be beneficial effects of immunotherapy with paternal lymphocytes [10].

Lymphocytes were obtained from heparinized peripheral blood by Ficoll-Paque centrifugation. After centrifugation the cells at the interface were washed with sterile saline and suspended in sterile saline. The prepared cell suspension was injected sub-cutaneously into the patients' forearms. The identical second course was conducted after confirming pregnancy. Serum zinc levels, Mixed Lymphocyte Reaction Blocking Factors (MLR-Bf) and sCD30 level etc have been considered as potential biomarker for indication and efficacy of paternal lymphocyte immunization in recurrent spontaneous abortion [11-13]. Adverse effects such as thrombocytopeni, anaphylactic reactions, autoimmune diseases, transmissible disease, graft-versus-host reaction, pre-eclampsia, intra-uterine growth retardation, neonatal thrombocytopenia, intracranial hemorrhage or blisters, scarring or granuloma in injection sites have been reported.

The first case-controlled study of immunotherapy for recurrent spontaneous abortions showed that the outcome of subsequent pregnancies was significantly improved by the injection of paternal lymphocytes as compared to the outcome after the injection of autologous cells [14]. In 1994, a meta-analysis of all placebo-controlled trials showed that allogeneic Lymphocyte Transfusion (LIT) significantly increased the chance of live birth with 16.3% (95% CI: 4.8–27.8%) among patients with primary RPL [15,16]. The use of LIT became a quite widespread and accepted treatment until 1999, at which time the results of a large placebo-controlled trial showed that LIT did not increase the chance of live birth compared with placebo but rather tended to decrease it [17]. This trial has been criticized for failure to exclude patients with autoimmunity and used purified peripheral blood lymphoid cells after overnight storage. It has been suggested that immunotherapy of women with certain auto antibodies [Anti-nuclear Antibody (ANA) and Anti cardiolipin Antibody (ACL)] could reduce the live birth rate, otherwise, lymphocytes used for transfusions stored overnight at 4°C before infusion causes loss of cell-surface CD200 and loss of efficacy [18].

The lymphocyte immunization indications are women with three or more consecutive spontaneous abortions or two recurrent spontaneous abortions with documented genetically normal fetus with the same partner (the clinical guidelines recommendation committee of the U.S. in 1997). To evaluate the efficiency of certain therapeutic approaches for recurrent miscarriages, embryonic karyotypes should be considered. Culture and karyotyping of miscarried pregnancies from women suffering RPL has detected a 29-57% abnormality rate [19,20]. Epidemiological studies suggested that the risk of subsequent pregnancy loss is approximately 24% after two clinical pregnancy losses, 30% after three and 40% after four consecutive spontaneous abortions [21]. A patient with two abortions is more likely to have a subsequent live birth than a patient with three or more abortions. After two clinical pregnancy losses, about 60%-70% success rate could be attained without any intervention [2]. Wegener S [22] described the overall success rate of LIT was about 75% in patients with 1-2 abortions, which could not show a benefit of LIT. A high success rate may be due to rigour cause screening, blood coagulation test during pregnancy and abnormal embryonic karyotype exclusion.

Immunomodulatory therapies may improve the live birth rate in appropriately selected patients, its efficiency need further

investigation. It is important to have better diagnosis of subsets that benefit from LIT before LIT indicated in the URPL aborters.

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