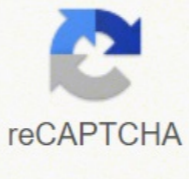




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Intrauterine administration of autologous peripheral blood mononuclear cells promotes implantation rates in patients with repeated failure of IVF–embryo transfer

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BACKGROUND: There are few effective approaches to infertile patients with repeated failure in IVF–embryo transfer therapy. Since recent evidence suggests that some populations of maternal immune cells positively support embryo implantation, we have developed a new approach using peripheral blood mononuclear cells (PBMCs). **METHODS:** Patients who had not experienced successful pregnancy despite four or more IVF–embryo transfer sessions were enrolled in this study ($n = 35$, 35 cycles). PBMCs were obtained from patients on the day of oocyte retrieval and were cultured with HCG for 48 h. Two days later, PBMCs were freshly isolated from patients again, combined with cultured PBMC and then administered to the intrauterine cavity of the patients. Blastocyst transfer was performed on day 5, and the success of implantation in the PBMC-treated group was compared with that in the non-treated group. **RESULTS:** Clinical pregnancy rate, implantation rate and live birth rate in the PBMC-treated group (41.2, 23.4 and 35.3%; $n = 17$, 47 and 16, respectively) were significantly higher than those in the non-treated group (11.1, 4.1 and 5.5%; $n = 18$, 49 and 18, respectively). **CONCLUSION:** Intrauterine administration of autologous PBMC may be an effective approach to improve embryo implantation in patients with repeated IVF failures.

Key words: embryo implantation/PBMC/IVF outcome

Introduction

Embryo implantation in the uterus is an essential phenomenon for mammals. In general, the endocrine system regulates endometrial differentiation to prepare for embryo implantation. Estrogen-primed endometrium is further differentiated to secretory endometrium by progesterone stimulation. In mice, it is widely accepted that endometrium can receive embryo implantation during a limited period, that is, the implantation window (Psychovos, 1993). Although human endometrium is also considered to have a limited period for embryo receptivity (Lessey, 2000), there have been few experiments investigating this concept. Using a primary monolayer culture of human endometrial epithelial cells and BeWo cell spheroids (John *et al.*, 1993), a human choriocarcinoma-derived cell line (Patillo and Gey, 1968), we observed that the adhesive ability of endometrial epithelial cells for BeWo cells was increased in those derived from women in the midsecretory phase (Kosaka *et al.*, 2003), supporting the idea that the receptive property of endometrial epithelial cells changes according to menstrual cycle (Lessey, 2000). It has been widely accepted that poorly developed endometrium is associated with infertility (Fanchin, 2001). Consequently, sex steroid hormone supplementation

has been clinically applied to infertile patients to induce adequate endometrial differentiation. However, when endometrial reactivity to sex steroid hormones is poor, this supplementation has little effect on endometrial function. Thus, alternative therapies other than endocrine approaches have been explored (Sher and Fisch, 2002).

Although the endocrine system plays a main role in preparing the endometrium for embryo implantation, there is evidence suggesting that the immune system also participates in supporting embryo implantation when the oocyte is fertilized. The presence of a developing embryo in the genital tract is one of the most important events for human females. More than two decades ago, early pregnancy factor was reported to be secreted from the developing embryo and to influence immune cell function and early events related to development and implantation of the embryo (Clarke, 1992; Morton *et al.*, 1992; Morton, 1998). We report that immune cells derived from pregnant mice directly promote endometrial differentiation at the peri-implantation period in a manner independent of the endocrine system (Takabatake *et al.*, 1997a,b). Later, CD4⁺(–)CD8[–] lymphocytes in the thymus derived from non-pregnant mice were also shown to enhance endometrial differentiation to induce embryo implantation, suggesting that

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