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Short Communication

Influence of Endometrial Immune Cell Plasticity on Implantation Success in Assisted Reproductive Cycles

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DESCRIPTION

Implantation is a highly coordinated biological event that requires precise interaction between the developing embryo and the maternal endometrium. While embryo quality remains an important determinant of reproductive success in assisted reproductive cycles, increasing attention has been directed toward the maternal immune system and its role in establishing pregnancy. The endometrium is not a passive structure during implantation; instead, it contains a dynamic population of immune cells capable of adapting their function in response to hormonal and embryonic signals. This ability, described as immune cell plasticity, has become an important topic in reproductive immunology [1].

Uterine natural killer cells represent the most abundant immune population within the secretory endometrium. Unlike peripheral natural killer cells that primarily function in cytotoxic defense, uterine natural killer cells exhibit a specialized regulatory phenotype [2]. They contribute to vascular remodeling, secretion of angiogenic factors, and modulation of trophoblast invasion. Their activity is tightly regulated by cytokines, hormonal signals, and interactions with decidual stromal cells. Abnormal activation or insufficient functional adaptation of these cells may interfere with implantation and early placental development [3].

Macrophages within the endometrium also demonstrate functional plasticity, shifting between pro-inflammatory and anti-inflammatory states depending on the microenvironment. These cells participate in tissue remodeling, debris clearance, and regulation of inflammatory signaling. During implantation, macrophages are generally biased toward a reparative phenotype that supports tissue remodeling and immune tolerance. Disruption of this balance may contribute to implantation failure or early pregnancy loss in some patients undergoing assisted reproductive treatment. Dendritic cells play a central role in antigen presentation and immune tolerance induction [4]. Within the reproductive tract, these cells interact with T lymphocytes to regulate adaptive immune responses. During the implantation window, dendritic cells contribute to the generation of regulatory T cells that suppress excessive immune activation against the semi-allogeneic embryo. Impaired dendritic cell function may reduce immune tolerance and negatively affect embryo attachment and invasion [5].

Regulatory T cells are essential for maintaining immune tolerance during pregnancy. These cells suppress excessive immune responses and help prevent rejection of embryonic tissue. Their expansion during the luteal phase is influenced by progesterone and local cytokine signaling. Reduced regulatory T cell activity has been associated in some studies with recurrent implantation failure and recurrent pregnancy loss. However, interpretation of these findings remains complex due to variability in immune assessment methods and patient populations. Hormonal regulation plays a central role in shaping endometrial immune plasticity. Estrogen and progesterone modulate cytokine production, immune cell recruitment, and tissue remodeling [6]. Progesterone in particular promotes a shift toward immune tolerance by influencing gene expression in stromal and immune cells. In assisted reproductive cycles using controlled ovarian stimulation, supraphysiologic hormone levels may alter the natural timing and magnitude of immune adaptation, potentially affecting implantation conditions [7].

Embryo-derived signals also contribute significantly to immune regulation. The preimplantation embryo releases cytokines, growth factors, and extracellular vesicles that interact with endometrial immune cells. These signals help identify the embryo as a compatible entity and initiate localized immune tolerance. Variations in embryonic secretory activity may influence immune cell behavior and implantation success. Poor-quality embryos may fail to generate adequate immunomodulatory signals, potentially reducing endometrial receptivity [8].

Chronic inflammatory conditions such as endometriosis, adenomyosis, and recurrent endometritis are associated with altered immune cell composition within the endometrium. These disorders often involve persistent activation of inflammatory pathways, increased cytokine production, and disruption of immune tolerance mechanisms. Women with such conditions may experience reduced implantation rates even

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when high-quality embryos are transferred during assisted reproductive cycles [9].

Metabolic health also influences immune plasticity within the reproductive tract. Obesity, insulin resistance, and dyslipidemia are associated with chronic low-grade inflammation that can alter immune cell function. These metabolic disturbances may shift macrophage and natural killer cell behavior toward pro-inflammatory phenotypes, potentially interfering with implantation processes. Nutritional status, physical activity, and systemic inflammation therefore represent important factors influencing reproductive immunology. Endometrial microbiota composition has been proposed as another factor influencing immune cell behavior. Microbial metabolites and bacterial-associated molecular patterns may interact with immune receptors, modulating cytokine production and immune cell differentiation. Although research in this area is ongoing, evidence suggests that microbial imbalance may contribute to inflammatory activation and impaired immune tolerance within the endometrium [10].

Assisted reproductive technologies may also influence immune cell dynamics. Hormonal stimulation protocols, embryo culture conditions, and cryopreservation techniques may indirectly affect endometrial immune responses. Frozen embryo transfer cycles, in particular, allow separation of ovarian stimulation from implantation, potentially resulting in a more physiologic endometrial environment in some cases. However, immune variability among individuals remains substantial.

CONCLUSION

Endometrial immune cell plasticity represents a dynamic and highly regulated process essential for successful implantation in assisted reproductive cycles. Uterine natural killer cells, macrophages, dendritic cells, and regulatory T cells collectively contribute to immune adaptation and tolerance. Disruption of this balance may negatively affect implantation outcomes, particularly in patients with inflammatory, metabolic, or reproductive disorders. Continued research integrating immunology, reproductive endocrinology, and molecular biology may improve understanding of implantation mechanisms and support more individualized approaches in assisted reproductive medicine.

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