Recurrent Pregnancy Loss through the Lens of Immunology

Evolutionary development of the immune system dates back to the emergence of life in the universe. Immune system emerges early in the course of embryogenesis; immune-restricted progenitor cells appear very early during development in the yolk sac and contribute later to the emergence of lymphoid and myeloid components of the immune system (1). Immune system consists of biological structures, entities, players and processes with a multiplex and intricate interaction with other body systems. It inspects and senses every subtle change in the expression level, stereochemical composition and conformation of the molecules and accordingly mounts regulatory responses. In physiological condition, immune system remains steady and delicately balanced; a small change in the normal physiological processes is concomitantly followed by immediate counter-regulatory mechanisms of the immune system leading to establishment of a new level of immunological balance.

Pregnancy, as the most prominent physiological condition associated with a new level of immunological balance, is preceded by vaginal insemination. Seminal plasma contains large amounts of transforming growth factor β and prostaglandin E capable of induction of regulatory T cells (Treg). Seminal fluid initiates a series of events leading to induction of tolerogenic dendritic cells competent to prime Tregs (2). Treg deficiency is associated with such pregnancy-related complications as unexplained infertility, miscarriage, and pre-eclampsia.

Within hours after fertilization and in order to adapt to such an immune-stimulatory condition as pregnancy, immune system deliberately creates early pregnancy factor (EPF) with potent immunomodulatory properties (3), a very early sign of pre-implantation immune adaptation to antigenically dissimilar embryo.

For successful implantation, extensive modification of endometrium at the cellular and molecular levels and intricate bidirectional communication between implanting blastocyst and the endometrium are required. Such communication is orchestrated by a complex and multilayer network of immune cells, chemokines, cytokines, growth factors and adhesion molecules. In this context, a set of pro-inflammatory TH1 cytokines work in concert in a tightly-regulated manner to establish endometrial receptivity and window of implantation. Chemokines and adhesion molecules mediate blastocyst apposition and adhesion to endometrium. And finally decidual immune cells, mainly uterine natural killer cells (uNK), dendritic cells, TH1 and Treg cells play an eminent role not only in mediating immune tolerance, but also in vascular remodeling and decidual development (4).

During pregnancy, the composition of decidual immune cells and cytokine profile gradually undergoes extensive modification and new functional synapses between fetal trophoblast and maternal immune cells are formed, supporting the fourth piece of conception. Plodding predominance of TH2 cytokines, stepwise decline in uNK cell and increase of Tregs population are among the hallmark of immune adaptation during pregnancy. Such complex modifications synergistically create a state of tolerance and form the basis of immunotrophism for embryo development (5).

The final act of the performance is initiated around parturition by an extensive influx of neutrophils and macrophages and a re-balancing process of cytokine profile toward TH1, when a set of pro-inflammatory cytokines and mediators are released leading to cervical ripening and labor.

As a matter of fact, a successful pregnancy is based, in essence, on highly harmonic spatiotemporal regulatory action of the immune network at the feto-maternal interface leading to endometrial receptivity and maternal tolerance. It is, thus, conceivable to imagine that immunologic disturbances not indemnified by the compensatory mechanisms are associated with reproductive failures during implantation and pregnancy.

Initially, recurrent pregnancy loss (RPL) was attributed mostly to such maternal factors as anatomic abnormalities, endocrine dysfunction or chromosomal aberrations. Gradually during the last two decades, such opinion lost its validity and it became clear that these factors do not account for miscarriage in a large percentage of women suffering from RPL. It is now evident that about 95% of clinically lost embryos in RPL patients have a normal karyotype and a significant proportion of these abortions are associated with immune etiologies. In fact, a great number of immunological imbalances has been documented in which development of fetus and placenta is affected by maternal autoantibodies or autoreactive cells leading to infertility or RPL. Similarly, alloimmune rejection-type activity of maternal humoral or cellular immunity accounts for a great proportion of RPLs (6).

Despite the undeniable impact of immune system in the course of pregnancy and great progresses that have been made over the recent years for documentation of immune etiology of a large percentage of RPL cases, most of the Iranian gynecologists still do not value reproductive immunology. This trend is also observed in Iranian scientific reproductive societies. Fortunately, global gynecologists' attitude toward reproductive immunology is going to be overwhelmingly positive and this science has evolved from basic research experiments to clinical applications in most part of the world for management of RPL and repeated implantation failure (7).

All in all, it is not imprudent to say that *it is time to see recurrent pregnancy loss in the light of immunology.*

References

1. Boiers C, Carrelha J, Lutteropp M, Luc S, Green JC, Azzoni E, et al. Lymphomyeloid contribution of an immune-restricted progenitor emerging prior to definitive hematopoietic stem cells. Cell Stem Cell. 2013;13(5):535-48.
2. Robertson SA, Prins JR, Sharkey DJ, Moldenhauer LM. Seminal fluid and the generation of regulatory T cells for embryo implantation. Am J Reprod Immunol. 2013;69(4):315-30.
3. Orozco C, Perkins T, Clarke FM. Platelet-activating factor induces the expression of early pregnancy factor activity in female mice. J Reprod Fertil. 1986;78(2):549-55.
4. Chaouat G. Inflammation, NK cells and implantation: friend and foe (the good, the bad and the ugly?): replacing placental viviparity in an evolutionary perspective. J Reprod Immunol. 2013;97(1):2-13.
5. Erlebacher A. Immunology of the maternal-fetal interface. Annu Rev Immunol. 2013;31:387-411.
6. Varla-Leftherioti M. Recurrent pregnancy loss Causes, controversies and treatment. 2nd ed. New York: CRC press; 2015. Chapter 27, The Immunobiology of Recurrent Miscarriage; p. 233-48.
7. Kwak-Kim J, Han AR, Gilman-Sachs A, Fishel S, Leong M, Shoham Z. Current trends of reproductive immunology practices in in vitro fertilization (IVF) - a first world survey using IVF-Worldwide.com. Am J Reprod Immunol. 2013;69(1):12-20.

Amir-Hassan Zarnani, D.M.T, Ph.D. *

Associate Editor of the Journal

* Reproductive Immunology Research Center, Avicenna Research Institute, ACECR, Tehran, Iran