The State of Peripheral Blood Natural Killer Cells and Cytotoxicity in Women with Recurrent Pregnancy Loss and Unexplained Infertility

Azam Azargoona, M.D.1, 2, Yasaman Mirrasouli, M.D.2, 3, Mahdieh Shokrollahi Barough, M.Sc.2, 4, Mehdi Barati, M.Sc.2, 5, Parviz Kokhaei, Ph.D.6, 7

1. Abnormal Uterine Bleeding Research Center, Semnan University of Medical Sciences, Semnan, Iran
2. Department of Infertility, Amir-AL-Momenin Hospital, Semnan University of Medical Sciences, Semnan, Iran
3. Student Research Committee, Semnan University of Medical Sciences, Semnan, Iran
4. Cancer Immunotherapy and Regenerative Medicine Department, Breast Cancer Research Center, Motamed Cancer Institute, ACECR, Tehran, Iran
5. Department of Immunology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
6. Cancer Research Center, Semnan University of Medical Sciences, Semnan, Iran
7. Immune and Gene therapy Lab, CCK, Karolinska University Hospital Solna, Stockholm, Sweden

Abstract

Background: The prognostic value of peripheral natural killer (pNK) cells, as a screening test in women with recurrent pregnancy loss (RPL) and unexplained infertility, is still a matter for discussion. The purpose of this study was to compare the percentage of circulating CD56+ NK cells, CD69 and perforin markers between women with unexplained infertility and RPL with the healthy control group.

Materials and Methods: In this case-control study, the percentage of CD56+ NK cells and activation markers (CD69 and perforin levels) in the peripheral blood were measured in 25 women with unexplained infertility, 24 women with idiopathic RPL and 26 women from the healthy control group, using specific monoclonal antibodies by flow cytometry.

Results: The percentage of CD56+ NK cells was significantly higher in patients with infertility in comparison with the healthy control group (P=0.007). There were not significant differences either in the total number of CD56+ cells between the RPL group and the control group (P=0.2) or between the RPL group and the infertile group (P=0.36). The percentage of CD69+ lymphocytes in RPL group was significantly higher than in the infertility group (P=0.004). There was a statistically significant difference in Perforin levels between RLP and control (P=0.001) as well as RPL and infertile (P=0.002) groups.

Conclusion: An increased percentage of CD56+ NK cells in patients with unexplained infertility, an elevated expression of CD69 on NK cells in patients with RPL and infertility and a high level of perforin on CD56+ cells in the RPL group might be considered as immunological risk factors in these women.

Keywords: CD56+, Infertility, Perforin, Peripheral Natural Killer Cell, Recurrent Miscarriage


Introduction

Infertility is defined as the failure of a couple to get pregnant after 12 months or more of having regular unprotected intercourse. Unexplained infertility is idiopathic and its cause remains unclear when the standard investigation of both male and female partner has made other infertility diagnoses impossible. Recurrent pregnancy loss (RPL), a heterogeneous circumstance often idiopathic, is described as three or more sequential miscarriages occurring before 20 weeks of gestation (1). However, the American Society of Reproductive Medicine (ASRM) has lately defined again RPL as two or more failed pregnancies and the American College of Obstetrician and Gynecologists has stated that the causes of recurrent fetal losses are similar in women who have had two or more miscarriages in comparison with women with three losses (2). The causes of RPL could be chromosomal abnormalities, uterine anomalies, endometrial infections, endocrine etiologies, antiphospholipid syndrome inherited thrombophilias, and alloimmune factors.

Among these suggested causes, only chromosomal abnormalities, antiphospholipid syndrome and uterine anatomic abnormalities are universally approved (3). One of these causes can be seen in about 50% of patients. How-