Journal of Blood Disorders, Symptoms & Treatments

Editorial Corner

NK cells and Unexplained Recurrent Pregnancy Loss, a Well-Known but Rarely Considered Association

This article was published in the following Scient Open Access Journal:
Journal of Blood Disorders, Symptoms & Treatments
Received September 06 , 2018; **Accepted** September 17, 2018; **Published** September 21, 2018

Pierpaolo Di Micco[1,3]*, Ida Strina[2] and Corrado Lodigiani[3]
[1]UOC Medicina, Ospedale Fatebenefratelli di Napoli, Italy
[2]University Department of Neuroscience, Reproductive Science, Odontostomatology; DAI Maternal Infant, Unit of Gynecology Obstetric, Sterility Center, Federico II University of Naples, Naples, Italy
[3]Thrombosis Center, Istituto Clinico Humanitas, Rozzano, Milano, Italy

Abstract

Recurrent pregnancy loss (RPL) is a daily intriguing work in women in reproductive age. Differential diagnosis should always be considered because RPL could be related to several clinical condition as chromosomal aberration, endocrine abnormalities, uterine malformations, uterine infections thrombophilia and so on. Immunological abnormalities have also been considered in this clinical setting both as chronic inflammatory diseases as abnormal levels of subset of immune cells or antigens. Immunological abnormalities in fact are frequently considered for unexplained RPL although a clear clinical and therapeutic approach actually is not available.

In this editorial corner most commonly associated immunological abnormalities associated to RPL as peripheral NK cells levels or impairment of lymphocytes T helper type 1 and 2 have been reported as well documented cause of RPL in selected population.

This alteration could better address the clinical management of RPL but should be better studied also from a prognostic point of view in future studies.

Editorial Corner

Recurrent pregnancy loss (RPL) represents a major health problem with two to three or more losses in up to 5% of women of reproductive age and it has been considered as one of the most common causes of female infertility [1].

Several reports identified several clinical condition and diseases potentially responsible of RPL such as endocrine diseases (e.g. ovarian dysfunction, anovulation, hypopituitarism, diabetes), uterine malformations, genetic alterations (e.,g. chromosomal aberrations), hypercoagulable state and thrombophilia (e.g. inherited thrombophilia, antiphospholipid syndrome, combined thrombophilia), chronic inflammatory diseases (in particular systemic lupus erythematosus), infectious diseases and immunological abnormalities [2-6].

A significant portion of unexplained pregnancy loss is associated with immune etiology in fact, and we may include immunopathological conditions as erythematosus lupus or antiphospolipid syndrome or autoimmune and cellular abnormalities.

Although at the beginning of the century several immune dysfunctions have been described in mice with RPL but the same dysfunctions were not confirmed in humans, recently further immune abnormalities were found in selected population of women with RPL.

In several reports in the Literature in fact an impaired ratio of T helper lymphocyte type 1 and type 2 or an increased percentage of NK lymphocytes have been associated to RPL [7]. However, it has always been difficult to establish a thorough magnitude of immune etiology of RPL because its incidence in each study may be different because of the adopted different inclusion and exclusion criteria.

From a pathophysiological point of view several abnormalities in immune balance have been underlined and reported as markers of RPL. The impairment of immunological functions of a pregnant woman has the recognition of paternal antigens present on the fetus and this mechanism is related to the following RPL [8]. Several immune functions as migration of immune cells, cytokine production and impaired lymphocytes T ratio have benn the most frequently underlined in the literature. Immune cells most frequently associated to migration to uterine district are peripheral blood monocytes

***Corresponding Author:** Pierpaolo Di Micco, MD, PhD, Fatebenefratelli Hospital of Naples, Italy,Email: pdimicco@libero.it

(PBMc) and Natural Killer cells (NKc), yet cytokines are mainly produced by PBMc and lymphocytes T helper. Moreover an impairment of levels of lymphocytes T helper type 1 and 2 has benn frequently reported in women with RPL [8]. Endocrine and paracrine productions of female sexual hormones seem to be also associated to the increase of NKc in the decidual endometrium during the implantation [9] so giving further attention to levels of peripheral NKc vs uterine NKc as potential responsible of abnormal immune response toward fetus [9,10].

So, as confirm levels of peripheral NKc have been found increased in selected populations of patients with RPL vs healthy subjects and vs patients with end stage kidney failure [11,12]. Moreover also other markers of immune activation in the same study were reported in patients with RPL vs controls as interleukin 4 levels, interleukin 4 antigens, transforming growth factor beta levels and trasforming growth factors beta antigens levels [11].

These alterations may be relevant from a clinical point of view too, actually in fact the percentage of unexplained RPL varies from 20 to 35% and immunological alterations seem to be to most involved. However a real magnitude of this recognized immunological abnormalities as the increase of peripheral NKc cannot be found actually because available studies are mainly retrospective or in selected populations. Of course the levels of increased peripheral NKc should be considered together to uterine, malformation, uterine infections, chromosomal abnormalities and thrombophilia in the evaluation of a patients with RPL.

On the other side besides these several immunological alterations have been identified, little is known from a therapeutic point of view. First of all although the reduction of levels of NKc seem to possible with the use of steroids, none reported an appropriated dose of steroids that can be used in this clinical setting and furthermore none suggested how this therapeutic approach can be monitored during the treatment. So haemocrome with total lypmhocytes count and a repetition of peripheral NKc levels have been considered but actually without any type of confirm from a clinical point of view. Thereafter also studies on the prognosis of women with RPL and increased peripheral NKc are treated with steroids or other drugs lacking in the Literature so underling that we are at the beginning of an unsolved problem.

In conclusion we can assert that immunological abnormalities other than immunological systemic disease should be involved in the pathophysiology of RPL in particular for cases with unexplained RPL; however appropriated clinical strategies and studies to identify, to treat and to monitor this clinical problem should be planned in next years.

References

1. Sarig G, Younis JS, Hoffman R, et al. Thrombophilia is common in women with idiopathic pregnancy loss and is associated with late pregnancy wastage. *Fertil Steril*. 2002;77(2):342-347.
2. Eldor A. Thrombophilia, thrombosis and pregnancy. *Thromb Haemost*. 2001;86(1):104-111.
3. Carp H, Salomon O, Seidman D, et al. Prevalence of genetic markers for thrombophilia in recurrent pregnancy loss. *Hum Reprod*. 2002;17(6):1633-1637.
4. Prandoni P, Tormene D, Simioni P, Girolami A. Venous thromboembolism, fetal loss and preeclampsia in pregnant women with congenital thrombophilia. *Clin Lab*. 2001;47(3-4):155-159.
5. Di Micco P, D'Uva M, Strina I, et al. Recurrent pregnancy loss and thrombophilia. *J Clin Med Res*. 2010 Feb; 2(1):18-22.
6. Di Micco P, D'Uva M. Recurrent pregnancy loss and thrombophilia. *The Open Atherosclerosis & Thrombosis Journal*. 2009;2:33-35.
7. Kwak-Kim J, Park JC, Ahn HK, et al. Immunological modes of pregnancy loss. *Am J Reprod Immunol*. 2010;63(6):611-623.
8. Laird SM, Tuckerman EM, Cork BA, et al. A review of immune cells and molecules in women with recurrent miscarriages. *Hum Reprod Update*. 2003;9(2):163-174.
9. Dosiou C, Giudice KC. Natural killer cells in pregnancy and recurrent pregnancy loss: endocrine and immunologic perspectives. *Endocrin Rev.* 2005;26(1):44-62.
10. Han G, Chen Y, Xu J, et al. The regulation of ovary and conceptus on the uterine natural killer cells during early pregnancy. *Reprod Biol Endocrinol*. 2017;15:73.
11. Zhu L, Aly M, Wang H, et al. Increased natural killer cell subestes with inhibitory cytokines and inhibitory surface receptors in patients with recurrent miscarriage and decreased or normal subsets in kidney transplants recipients late post transplant. *Clin Exp Immunol.* 2018;193(2):241-254.
12. Chen X, Mariee N, Jiang L, et al. Measurement of uterine natural killer cell percentage in periimplantation endometrium from fertile women and women with recurrent reproductive failure: establishment of a reference range. *Am JObstetric Gynecol* .2017;217(6):680-686.