Recurrent miscarriage: Are NK cell subsets a good predictor?

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Recurrent pregnancy loss, recurrent miscarriage, and recurrent implantation failure, regardless of what the terminology is used, is a very challenging and frustrating condition for both the clinicians and patients attempting to reproduce.[1,2] From a clinical viewpoint and patients' wishes, physicians always have to deal with stressed couples who are frequently overwhelmed by the above-mentioned situation. Since there are many underlying causes (abnormal chromosomes, endocrinological disorders, and uterine abnormalities) and some are uncertain (immunological problems such as autoimmune antibodies, anti-phospholipid syndrome, thrombophilias, hemonatural killer cells, regulatory T cells, tumor necrosis factor α, cell-derived microparticles, leptin, certain glycoproteins, and cytokines) contributing to the recurrent pregnancy loss,[3,4] any attempt to clarify the cause of recurrent miscarriage is welcome. We are happy to learn Dr. Adib Rad's article, which has been published in the December issue of the *Journal of the Chinese Medical Association* last year to investigate the alternation of the natural killer (NK) cell subsets and cytokines on the impact of recurrent miscarriage.[5] The authors used a case-control study to explore the potential markers such as NK cell subsets and cytokines (interleukin [IL]-2 and IL-12) in the prediction of the women who might have a higher risk of recurrent miscarriage.[5] The authors found that an increased percentage of either $CD56^+CD16^+$ (a cut-off value of ≥ 5.25%) or $CD56^+CD16^-$ (≥3.4%) cells in the peripheral blood was found in the women with recurrent miscarriage and claimed that their findings can be used to establish prospective researches to recognize the predictive value of these parameters in the evaluation of women with recurrent miscarriage.[5] We congratulated the success and excellent works from the authors. However, some questions are raised and we hope to receive the authors' response.

In the "Results" section (page 1068),[5] the authors wrote that "the mean of living child in the control group and abortion in the case group was 1.45 ± 0.50 and 2.75 ± 1.01, respectively (p = 0.0001)".[5] What did the authors mean? Did the authors mean that women in the control group had delivered a mean of 1.45 living babies (parous 1.45) and women in the recurrent miscarriage group had abortion with a mean of 2.75?

In the "Methods" section (page 1066), why the authors decide to obtain the peripheral blood samples from all women at their follicular phases of the menstrual cycles? We are wondering why the authors did not perform this examination in the mid-luteal phase of the menstrual cycle between day 7 and day 10 after the mid-cycle luteinized hormone surge, which is well-known for the occurrence of implantation.[3] It is well-known that NK cells varied during the menstrual cycles.

Finally, recurrent miscarriage women have been reported to show up-regulated cytotoxic NK cells that are suspected to play a causal role in abortion. According to the findings of the authors, can the increased percentage of $CD56^+CD16^+$ (≥5.25%) or $CD56^+CD16^-$ (≥3.4%) cells be a representative of the up-regulated cytotoxic NK cells?

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