Progesterone may be why pregnant women are more vulnerable to certain infections

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Women who are pregnant or using synthetic progesterone birth control injections have a conspicuous vulnerability to certain infections including malaria, Listeria, HIV, and herpes simplex virus. A new research report appearing in the March 2013 issue of the *Journal of Leukocyte Biology* offers strong evidence for a possible explanation: the progesterone receptor, a pregnancy hormone sensor, targets a part of the immune system responsible for protection against these and other invaders. In addition to helping explain why some women are more vulnerable to certain infections, it also sheds light on why some autoimmune diseases, notably rheumatoid arthritis and multiple sclerosis, often go into remission during pregnancy.

"We hope that continued work in this area will ultimately yield better approaches to the prevention of immunological complications of pregnancy, safer and more effective forms of hormonal birth control and novel biological targets for the treatment of autoimmune diseases," said Grant C. Hughes, M.D., a researcher involved in the work from the Division of Rheumatology and Department of Immunology at the University of Washington in Seattle, WA.

To make their discovery, scientists used two groups of mice. The first group had a mutated progesterone receptor, or PR gene, which rendered the mice's bodies incapable of sensing progesterone through PR (PR knockout mice). The second group was comprised of normal mice. After various forms of immunization, antibody responses were tracked. When compared to normal mice, PR knockout mice produced much higher

antibody levels, but only in response to forms of immunization requiring T cells, a cell type that normally boosts antibody production by B cells. This prompted a closer look at B and T cells from the PR knockout mice. The researcher saw that when stimulated in the test tube, knockout B cells showed normal, if not slightly less, antibody production compared to controls. On the other hand, knockout T cells stimulated in the test tube showed a conspicuous over-production of interferon-gamma, an inflammatory molecule involved in fighting off pregnancy-associated pathogens and in shaping protective antibody responses. Adding progesterone to the test tube blocked interferon-gamma in normal T cells, but not in PR knockout T cells. This suggests that progesterone suppresses interferon gamma in T cells through their PR. To sort out which aspects of the abnormal antibody responses in PR knockout mice were due to T cells, researchers immunized two groups of normal mice, one transplanted with responder T cells from PR knockout donors, the other with responder T cells from normal donors. Just like in PR knockout mice, normal mice transplanted with PR knockout responder T cells showed much higher antibody levels than normal mice.

"Pregnancy and hormones have long been known to influence immune responses, but these processes have been poorly understood, said John Wherry, Ph.D., Deputy Editor of the Journal of Leukocyte Biology. "This new work is significant for two reasons. First, the identification of progesterone receptors as a mechanism of immune modulation during pregnancy sheds light on the pregnancy-immune phenomenon, and second, these studies define a potentially new target to modulate autoimmunity and immune-mediated problems during pregnancy."

More information: Grant C. Hughes, Edward A. Clark, and Alan H. Wong. The intracellular progesterone receptor regulates CD4+ T cells and T cell-dependent antibody responses. J Leukoc Biol March 2013 93:369-375, doi:10.1189/jlb.1012491