Is the immune system (i.e., autoimmunity and inflammation) really irrelevant to IVF success?

Norbert Gleicher, MD,
Medical Director and Chief Scientist, The Center for Human Reproduction – New York,
President, The Foundation for Reproductive Medicine,
Professor (Adj.) Laboratory for Stem Cell and Molecular Embryology, The Rockefeller University,
Professor (Adj.) Department of Obstetrics & Gynecology, Medical University Vienna, Austria

Pregnancy is a time-limited paternal semi-allograft, in normal pregnancy tolerated by the maternal immune system for an average gestational period of 40 weeks. That a normally functioning maternal immune system, therefore, is essential for establishment and maintenance of normal pregnancy should be obvious. Many clinical reproductive endocrinologists, surprisingly, yet still consider the maternal immune system as irrelevant to IVF success.

Though how the normal maternal immune system reprograms itself from rejection to tolerance in preparation for, or as part of, the implantation process, is not fully understood, it has become increasingly clear that successful and timely establishment of tolerance toward the implanting embryo is an essential step in successful implantation and early pregnancy maintenance. Failure of establishing proper timely tolerance will lead to implantation failure and/or increased miscarriage risk, as the maternal immune system, at least partially, still sees the implanting embryo (and early pregnancy) as a semi-allograft, and attempts to reject it in an allogeneic immune response.

There is increasing evidence that hyperactive maternal immune systems, as, for example, seen in association with autoimmunity and severe hyperallergenic states, lose the ability to fully reprogram themselves from being rejective to being tolerant and, therefore, are associated with implantation failure and increased miscarriage risks. We, for example, have been able to demonstrate that elevated CRP greatly reduces IVF chances, while elevations in IL-6 are highly associated with miscarriages.

If such hyperactive immune systems are, however, medically suppressed in their allogeneic immune response toward the paternal semi-allograft until secondary tolerance-inducing mechanisms (especially microchimerism) come on line in the early 2nd trimester, pregnancies enter a quiet period of satisfactory temporary tolerance. The so-induced tolerance, indeed, benefits the mother beyond just establishing tolerance to the fetal semi-allograft. It appears that here induced tolerance pathways of the immune system are also beneficial to self-tolerance (i.e. autoimmunity). With the best evidence being that, once the initial miscarriage risk is overcome, autoimmune diseases in pregnancy actually improve clinically until later in pregnancy, when the temporary tolerance of pregnancy in so-affected patients often prematurely terminates, leading to the well-known complications of premature labor, preeclampsia/eclampsia and gestoses of pregnancies. All of these major late pregnancy complications are now increasingly considered manifestations of premature termination of tolerance and of an allogeneic immune response of the maternal immune system against the fetal semi-allograft. Such responses, thus, appear in predisposed patients at start and end of gestational tolerance.

In other words, women who at the beginning of pregnancy experience difficulties in establishing tolerance, are also at increased risk for developing premature termination of temporary tolerance. It is for this reason that practically all autoimmune diseases are characterized by premature labor and peripartal flair risks.

The recent literature offers interesting new evidence that normal pregnancy, indeed, established specific tolerance pathways. So, for example, a recently published study in Science demonstrated that certain helminth (parasites) favor fecundity in comparison to other helminths, suggesting that the former in the process of establishing a symbiotic relationship with their host, induce tolerance pathways in female immune systems, which favor pregnancy (i.e. tolerance toward the fetal semi-allograft). Concomitantly, the New York Times recently reported on a developing underground medical industry in the U.S., which propagates infections with helminths as treatment of intractable autoimmune diseases, thus mimicking above noted concept that proper induction of tolerance pathways toward the fetal semi-allograft also benefits self-tolerance in autoimmune diseases.

The most startling new evidence for the possibility of inducing of such tolerance pathways in pregnancy by pharmacological means are, however, a series of recent reports from all over the world (in different racial populations), all reporting that Influenza vaccinations during pregnancy reduce late complications of pregnancy, including premature labor, by up to 50%. These observations are in many ways groundbreaking because they come from large population studies from all corners of the world, and not only suggest a very inexpensive way of radically improving perinatal risk factors, leading to millions of perinatal deaths annually; but also because they suggest a rather simple and inexpensive way to potentially augment poor tolerance induction and premature termination of tolerance in women at risk.

Translational relevance: Recent suggestions pointing toward specific tolerance inducing immune pathways in pregnancy point toward potential inexpensive pharmacological methods of inducing such tolerance inducing pathways not only in female infertility and in association with late pregnancy complications but also in autoimmune diseases and allogeneic organ and tissue transplantation.