What makes a successful pregnancy?

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Fertility problems, recurrent miscarriages, and pregnancy complications can occur when maternal immunological tolerance of the fetus is impaired. Gérard Chaouat and colleagues from Inserm et Assistance Publique et Université Paris Sud Orsay, Hopital Antoine Bèclère, Clamart Cedex, France (now in Hopital Saint Louis, Paris), trace the evolution of the science of reproductive immunology to show how the current understanding of maternal-fetal tolerance/dialogue has developed, and its implications for the treatment of infertility disorders. Their study appears in a topical issue of *Advances in Neuroimmune Biology* on maternal-fetal interactions.

In the earliest era of reproductive immunology, immunologists searched for generalized immune suppressive activity to explain why the embryo's tissue is not rejected by the mother during pregnancy. Researchers soon realized that systemic immune suppression was not compatible with maternal capacity to reject paternal strain tissues, and it became recognized that some form of active maternal recognition is active in pregnancy. "There is no 'tolerance,' as is often written but indeed at least a part of the maternal immune system is stimulated and actively interacts with the fetal-placental unit," says Dr. Chaouat.

The active involvement of the maternal immune system was reinforced by the discovery that pre-immunization of abortive mouse mating combinations against paternal major histocompatibility complex (MHC) class 1 leads to prevention of fetal loss. This led to an emergence of interest in cytokine expression at the fetal-maternal interface, and the realization that while some cytokines were useful for pregnancy, others

were detrimental. A similar discovery found that although natural killer (NK) cells can be abortifacient if improperly activated, they are normally useful and necessary for pregnancy, implantation, and local uterine vascular transformation.

Dr. Chaouat and his colleagues describe how his team at the Embryo Implantation Control project, a large scale collaborative EEC network program to support research on female infertility, have studied the control of NK activation by various interleukins (notably the interleukin (IL)-12, -18 NK tripod) as well as tumor necrosis factor-related weak inducer of apoptosis (TWEAK) in mice and humans. In both mouse and human experiments, they have discovered that TWEAK plays a role as an immunoregulator against local cytotoxicity in order to protect the embryo.

Signals emitted by the embryo itself play a role in implantation and thus can influence implantation rates. In a pilot study the researchers measured the cytokine content of follicular fluid (FF) after oocyte collection and traced the fate of the subsequent embryos. "The most salient result of these studies was the prediction of good quality and implantation level," says Dr. Chaouat. "The level of granulocyte colony-stimulating factor (G-CSF) in individual follicular fluid samples was correlated with the implantation potential of the corresponding embryo in both natural and hyperstimulated cycles. In addition, we found that a combination of both FF G-CSF and IL-15 was the optimal model to predict birth specifically in monitored natural cycles, while IL-15 was undetectable in hyperstimulated cycles. Such differences suggest that immune cell trafficking may be involved in the establishment of oocyte competency for implantation."

Recent work by Dr. Chaouat and colleagues centers on the discovery of biomarkers for optimal uterine receptivity and oocyte competence to improve the efficiency of assisted reproductive technology (ART).

"Quantification of IL-18, TWEAK, and IL-15 mRNA expression may be useful for physicians. Follicular concentration of G-CSF appears as a useful biomarker of oocyte competence before fertilization," Dr. Chaouat concludes.

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