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Can tacrolimus treatment affect pregnancy outcomes in the presence of immune maternal abnormalities?

Maternal immune abnormalities can either be the cause or the consequence of current or previous pregnancies. The etiology of pre-gestational immune maternal disorders is variable depending on genetic and environmental factors. Aberrant maternal inflammation during pregnancy is often linked to the etiology of IUGR and pre-eclampsia. Women with IUGR and/or pre-eclampsia have a heightened systemic inflammatory milieu characterized by high levels of circulating proinflammatory cytokines. Severely pre-eclamptic women may encounter disseminated intravascular coagulation with widespread microvascular occlusive thrombi leading to renal and hepatic failure, placental and cerebral infarctions and seizures. Recent evidence suggests that defective spiral artery remodeling in animal models of pre-existing IUGR and pre-eclampsia are causally linked to abnormal activation of uterine leukocytes and placental macrophages. To be defined are the exact mechanisms underlying the pathology of IUGR and pre-eclampsia and their association with pre-existing anomalous maternal immune adaptation to pregnancy. Human and animal studies revealed decreased local and systemic maternal levels of immuno-protective/regulatory molecules in IUGR and pre-eclampsia compared with uncomplicated pregnancies. We were the first to demonstrate that the use of peri-conceptional sub-clinical dosages (0.05-0.1mg/kg/day) of tacrolimus is beneficial in treating repeated implantation failure (RIF) significantly minimizing incidence of adverse pregnancy outcomes (APOs) in the obese and diabetic subjects. Similarly, the peri-conceptional administration of tacrolimus in women with RIF revealed a casual association between aberrantly elevated Th1:Th2 peripheral blood lymphocyte ratios and poor pregnancy outcomes. The clinical value of this approach in the preventive management of RIF and APOs stems from the fact that immunological defects which arise during embryo implantation induce ripples effects with adverse materno-fetal consequences affecting later gestation as well as the immediate post-natal and long-term complications especially those related to obesity, cardiovascular and metabolic disorders, highlighting the significance of this event for pregnancy success and long term health management. It has been our experience that the use of immunosuppression successfully reduced the risk and incidence of APOs in immune-complicated pregnancies.

Most pre-gestational immune maternal abnormalities are multi-systemic autoimmune in nature requiring variable forms of immunosuppression. Although animals treated with tacrolimus have markedly improved lymphatic function, the use of clinical dosage of tacrolimus (3-5mg/kg/day) activates the renal sodium chloride co-transporter to cause hypertension hence the compound is classified as pregnancy class C by FDA. Important to clinical outcome in tacrolimus monotherapy is maintaining sufficient low dose of the compound in blood (0.23-0.6 ng/ml). The rate of hepato-renal excretion of tacrolimus is dependent upon serum concentrations of total bilirubin (2.0-9.9mg/dL), free bilirubin (10mg/dL) and serum creatinine (2mg/dL). Therefore, maintaining adequate hepato-renal functioning is integral to clinical outcome under tacrolimus monotherapy. Additionally, immunosuppression with tacrolimus may lead to a catabolic microbial profile in the gut, which may influence development of diabetes after soft organ transplant. Therefore, modulation of the microbiome with probiotics may help in minimizing adverse long-term

effects of the tacrolimus-mediated immunosuppression. We are currently investigating the long-term effects of tacrolimus monotherapy in mitigating the severity and incidence of long-term maternal and fetal health adversities. More data will be available in the near future.