**Intralipid therapy for recurrent pregnancy loss – controversies and future directions**

J Braverman, DR Ritsck

Braverman Reproductive Immunology PC, Woodbury, New York, USA

Intralipid is a 20% fat emulsion containing soybean oil triglycerides that was developed as a source of parenteral nutrition for patients unable to tolerate an oral diet. Immunomodulatory functions of Intralipid infusions were subsequently noted and Intralipid infusions, touted by many as an inexpensive alternative to IVIG, are now widely used to treat recurrent pregnancy loss.

While Intralipid infusions have been used for years in women experiencing recurrent pregnancy loss with anecdotal success, a satisfactory explanation for its therapeutic effects has been largely lacking. We will discuss controversies regarding its potential immunological mechanisms of action. There are several studies that demonstrate inhibitory effects of Intralipid on NK cell cytotoxicity, but there is so far no satisfactory description of the mechanism by which this effect is achieved. It is also not clear if Intralipid-mediated suppression of NK cell cytotoxicity is a relevant mechanism for its effects on preventing immunological pregnancy loss.

Alternatively, Intralipid’s effects may be mediated through metabolic effects on T cells. While resting T cells have a relatively low metabolic demand and use a balance of glucose, lipids, and amino acids as their metabolic fuel, activation of T cells causes them to undergo a dramatic metabolic reprogramming. While activation of effector T (Teff) cells of the Th1, Th2 and Th17 induces a decrease in fatty acid oxidation (FAO) and shift glucose metabolism away from oxidative phosphorylation and towards glycolysis, regulatory T (Treg) cells conversely rely heavily on FAO, and not on glycolysis, for fuel. The distinct metabolic differences between Treg and other T cell lineages may provide a target for selective immunomodulation that could be exploited therapeutically. Recent studies in fact have demonstrated that addition of exogenous fatty acids to T cells during activation inhibits differentiation of Teff cells and favors differentiation of Treg cells. Additionally, metformin increases Treg cell generation by binding to and activating AMP kinase, which in turn inhibits mTOR and causes a decrease in glycolysis and an increase in FAO. Thus, Intralipid infusion may function as one arm of an immunometabolic approach to promote Treg cell-mediated tolerance of the semi-allogenic embryo and efficient embryo implantation.

While there are obvious differences in their biochemical composition, Intralipid infusions are promoted by many clinicians as an inexpensive and effective functional alternative to IVIG. We will discuss this controversial idea informed by both the literature and our extensive clinical experience with both Intralipid and IVIG, including evaluation of our own data.

Finally, we will discuss areas for future research including the use of alternative intravenous fat emulsions containing higher ratios of ω-3 to ω-6 fatty acids.