

Problem: Embryo loss during early pregnancy contributes to infertility. A portion of these losses are hypothesized to be immune mediated but little is known about the immune cell responses to the presence of the embryo. This study tested the hypothesis that endometrial resident immune cells are induced to a tolerogenic phenotype by signals emanating from the developing conceptus.

Method of Study: Uterine tissue was collected from Holstein dairy heifers on Day 17 of the estrous cycle and Days 17 and 20 of early pregnancy. Tissues were labeled with antibodies against CD47 and Indoleamine 2,3-dioxygenase (IDO) and labeling intensity was analyzed using ImageJ software (n=5 heifers/status/Day). In addition, abundance of mRNA for CD172a and CD47 were analyzed in RNA extracted from whole endometrium by quantitative PCR (n=7-9 Day 17 cyclic, n=6 Day 17 pregnant and n=5 Day 20 pregnant). Results were analyzed using MIXED procedures of SAS using preplanned orthogonal comparisons.

Results: Endometrial labeling intensity for CD47 was greater ($p=0.05$) in endometrium from pregnant compared to cyclic heifers. Differences in labeling intensity were greatest in the shallow stroma and shallow glands ($p<0.05$). Labeling intensity for IDO staining was greater ($p<0.05$) in endometrium from Day17 pregnant heifers compared to Day17 cyclic heifers. Among pregnant heifers, labeling intensity was almost 3 fold greater at Day 17 versus Day 20 ($p<0.01$). Differences in IDO labeling intensity were greatest in the luminal epithelium, but were also detected in the shallow glands, deep glands and myometrium. No differences were observed in total endometrial mRNA abundance for CD47 and CD172a.

Conclusions: Results presented here support the hypothesis that conceptus signals affect resident immune cells at very early stages of pregnancy. We hypothesize that increased CD47 expression interacts with its receptor, CD172a, to induce inhibitory signals via Immunoreceptor Tyrosine based Inhibitory Motifs (ITIM). This interaction is known to bring about cell-cell adhesion and T cell inactivation. Increased IDO expression may induce production of kynurenine, a ligand for the Aryl Hydrocarbon Receptor (AhR) and is involved in Regulatory T cell generation. Thus, during early pregnancy in cattle, embryonic signals, including IFN tau, may promote development of tolerogenic immune phenotype for successful establishment of pregnancy.