



Figure S1 (A) Canonical pathways identified by ingenuity pathway analysis as likely regulated by Progesterone dose. Ratio refers to the number of genes with an expression/total number of genes that belong to the pathway. (B) Natural Killer (NK) Cell pathway. The inhibitory cell surface receptors of NK cells are characterized by intracytoplasmic immunoreceptor tyrosine-based inhibition motifs (ITIMs). They act by antagonizing the activating pathways through protein tyrosine phosphatases (PTPs). Several signaling components are substrates for protein tyrosine kinases (PTKs) of the activating receptors and the protein tyrosine phosphatases (PTPs) of the inhibitory receptors. Such common substrates include spleen associated tyrosine kinase (SYK) and Zeta Chain of T Cell Receptor-Associated Protein Kinase 70 (ZAP70). Phosphorylation status of these molecules determines the activating/inhibiting outcome. When present, bars close to the gene, from left to right, represent groups 2.5, 5, 10, 40 and control, respectively. Red bars represent up-regulation, while green bars represent down-regulation compared to 40 mg group. KIR-L and CD94/HKG2A receptor SHP are up-regulated and activate SHP complex, which inhibits downstream pathway to cytotoxicity and cytokine release. KIR-L/KIR2DL5: killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 5A; NKG2A: killer cell

lectin-like receptor subfamily C, member 1-like; CD94: killer cell lectin-like receptor subfamily D, member 1; SHP: a complex with protein tyrosine phosphatase, non-receptor Type 11 (PTPN11) and protein tyrosine phosphatase, non-receptor Type 6 (PTPN6). EAT-2: SH2-domain containing 1B; SLP-76: lymphocyte cytosolic protein 2 (SH2) domain, sterile alpha motif; VAV: vav one guanine nucleotide exchange factor; LCK/Fyn: lymphocyte-specific protein tyrosine kinase/FYN oncogene related to SRC, FGR, YES. (C) LIF/JACK/STAT signaling. The figure displays gene expression in the Leukemia Inhibitory Factor (LIF) signaling pathway. Bars close to the gene name, from left to right, represent groups 2.5, 5, 10, 40 mg and control, respectively. Red bars represent up-regulation, while green bars represent down-regulation. IL-15 activates GPI30, which is part of the LIF receptor, and phosphorylates and SHP2 (SH2-domain-containing tyrosine phosphatase). In the 40 mg group, SHP2 is up-regulated and inhibits Janus Kinase 1 (JAK1). Low doses of progesterone (≤ 5 mg) have the opposite effect. Suppressor of cytokine-signaling 1 (SOCS1), Signal transducer and activator of transcription 3 (STAT3) and tyrosine kinase 2 (TYK2), LIF and LIF receptor were not significantly different among groups.