Overweight and obesity increase endometrial cancer risk, but it is still unclear how obesity alters the benign endometrium to promote endometrial carcinogenesis. We hypothesized that increased adiposity alters the metabolism of the endometrium and decreases the protective activity of progesterone, resulting in a heightened susceptibility to carcinogenesis. To simulate adiposity, primary human benign endometrial organoids, consisting of both epithelial and stromal cells, were cultured with increasing numbers of human adipose spheroids in the presence of cyclic levels of estradiol, progesterone, and testosterone for 14 days. RNA-sequencing analysis revealed dysregulation of pathways including chromatin remodeling, angiogenesis, metabolism, and metal ion response pathways in endometrial organoids cocultured with 30 adipose spheroids. Strikingly, some of the most significantly downregulated genes included the metallothionein (MT) family of genes, including MT1A, MT1M, MT1X, and MT2A. MTs are important molecules that regulate metal ion balance in the cell, as well as detoxifying heavy metals and reactive oxygen species. Hormonal regulation of MTs in the endometrial organoids was confirmed, with estrogen and progesterone increasing MT expression by 2- to 10-fold. We also observed a non-significant downregulation of the endometrial progesterone response in the presence of 30 adipose spheroids, including decreased expression of HSD17B2, IGFBP1, PAEP, PRL, SPP1, and FOXO1. In summary, this study revealed that high adiposity alters endometrial gene expression, including a downregulation of MTs, and may decrease the endometrial progesterone response. Further investigation will determine the extent to which MT dysregulation by adiposity increases oxidative stress in the endometrium.