Neonatal exposure to medroxyprogesterone acetate alters canine uterine development

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A simple, permanent, non-surgical method for sterilizing dogs would benefit both animals and society. Previous work from co-investigators has shown that neonatal administration of progestins can permanently block uterine gland formation in sheep and mice, creating a uterine gland knock-out (UGKO) phenotypic model and inducing sterility in adult animals. The objective of this study was to test the hypothesis that neonatal progestin administration in the dog alters uterine development, with particular emphasis on uterine gland formation.

Seven mixed-breed female puppies were given either a time-released progestin (n=4), medroxyprogesterone acetate (MPA; 10 mg/kg IM), or saline (n=3) at 5 days of age. Dosing was repeated in the same manner when body weight tripled (average of 2.5 weeks of age). Serum MPA levels were determined at multiple time points to ensure adequate delivery of the drug. Ovariohysterectomy (OVH) was performed at seven weeks of age and uterine tissues were examined. Uterine gland development and epithelial proliferation were assessed in the following manner: tissues were stained with hematoxylin and cross-sections were examined using the Aperio® imaging system (Leica Microsystems, Inc., Buffalo Grove, IL) from which gland penetration measurements were obtained. Additionally, uterine cross sections were stained with POPO-1 to visualize cell nuclei, cytokeratin 8 (CK8) as an epithelial marker and proliferating cell nuclear antigen (PCNA) as a marker of cell proliferation. Primary antibodies were localized using fluorochrome-labeled secondary antibodies in order to produce target-specific signals at defined emission wavelengths: A490 (POPO-1), A568 (CK8), A594 (PCNA). Images were obtained using a Nuance FX multispectral imaging system (Caliper Life Sciences, Hopkinton, MA). Spectrally unmixed images were analyzed using Cell Profiler and Cell Profiler Analyst software (Broad Institute, Cambridge, MA). Quantitative data were subjected to analyses of variance. No effects of treatment on uterine gland penetration depth were identified. However, a treatment by cell-compartment interaction was detected (P < 0.01) for PCNA labeling index, indicating compartment-specific reductions in cell proliferation associated with MPA exposure. While uterine gland development was not inhibited overtly, MPA did reduce canine endometrial cell proliferation in both glandular and luminal epithelial compartments. Thus, strategic neonatal progestin exposure holds promise as a tool for programming canine endometrial development and function.

Keywords: Uterus, medroxyprogesterone acetate (MPA), canine, neonate, development