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Pregnant Mare and Perinatology

Effects of High and Low Progestin Concentration during the Early Luteal Phase on Endometrial Function in Early Pregnant Mares

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Progesterone prepares the endometrium for pregnancy. This paradoxically requires down-regulation of progesterone receptors in endometrial epithelia as prerequisite for the expression of pregnancy-associated proteins (Spencer and Bazer, Frontiers in Bioscience. 2002;7:1879-98). We investigated effects of altered peripheral progestin concentration in early luteal phase mares on endometrial function on day 14 of pregnancy. Genitally healthy oestrous mares (n=8; age 4 to 14 years) were inseminated with 500 million progressively motile spermatozoa at 48h-intervals until ovulation. Mares were treated with either altrenogest (0.044 mg/kg once daily orally) on days 5 to 10 after ovulation (ALT), cloprostenol (125 mg once daily intramuscularly) on days 0 to 3 after ovulation (CLO) or left untreated (control). ALT and CLO treatment aimed at increasing and decreasing total peripheral progestin concentration, respectively. Every mare received each treatment in consecutive cycles at random order. Blood for determination of progesterone concentration was collected once daily. Between days 10 and 14 after ovulation, transrectal ultrasonography was performed for detection of a conceptus and in pregnant mares, endometrial cells for RT qPCR, intrauterine fluid for analysis of amino acid concentrations and an endometrial biopsy for immunohistological examination were collected on day 14. Endometrial expression of mRNA cyclooxygenase-2 (COX-2), progesterone receptor, estradiol receptor, prostaglandin E synthase (PGES), prostaglandin F synthase (PGFS), and uteroferrin were analysed by RT qPCR. Expression of progesterone receptors in the endometrium was determined by immunohistochemistry. Statistical analysis was performed by ANOVA (general linear model for repeated measures with treatment and day as between subject factors). Values are given as mean ± standard error of mean. Progesterone concentration from day 0 to 14 after ovulation was lower after CLO than after ALT and control treatment ($p<0.001$). In the luminal endometrial epithelium, percentage of cells stained positive for the progesterone receptor was higher ($p<0.05$) after CLO (84±2%) than ALT (71±5%) and control treatment (73±4%). CLO treatment increased endometrial mRNA of uteroferrin and estradiol receptor but decreased PGFS mRNA in comparison to control ($p<0.05$). ALT treatment increased endometrial uteroferrin mRNA ($p<0.05$) but did not affect expression of any other candidate genes compared to control. Concentration of amino acids isoleucine (ALT 3.0±0.6, CLO 1.9±0.2, control 2.2±0.3 mg/100ml) and lysine (ALT 6.4±1.9, CLO 2.7±0.5, control 4.0±1.2 mg/100ml) in uterine fluid was lower ($p<0.05$) in CLO than ALT and control treated mares. Concentration of other amino acids was not influenced. In conclusion, CLO treatment during the early luteal phase impaired corpus luteum function, resulting in lower plasma progestin concentration and higher expression of endometrial progesterone receptors on day 14. The lesser down-regulation of endometrial progesterone receptors influenced endometrial function with regard to gene expression and amino acid secretion in early pregnant mares, potentially affecting further conceptus development.

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