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Antiluteogenic effects of prostaglandin F2α

Efeito antiluteogênico da prostaglandina F2α

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Abstract

PGF2α has been studied for many years for its ability to induce luteolysis in natural cycles and after exogenous administration. In the present review, we will discuss the results of recent studies that found a novel effect of exogenous administration of PGF2α when given serially during the first days of diestrus: to prevent the formation of the corpus luteum and induce a new estrus. This phenomenom has been named "antiluteogenesis".

Keywords: antiluteogenesis, corpus luteum, equine, PGF2α.

Resumo

A Prostaglandina F2α tem sido investigada for muitos anos como um potente agente luteolitico. Esta breve revisão se foca em um fenômeno somente descrito recentemente: a habilidade da PGF2α de prevenir a formação do corpo luteo quando administrada serialmente durante os primeiros dias do diestro. Este fenômeno é então chamado de efeito antiluteogênico.

***Palavras-chave**: antiluteogênesis, corpo luteo, equino, PGF2α.*

Introduction

The results presented in the early studies in the 1970's provided the basis for the assumption that PGF2α formulations would not induce luteolysis or affect the function of the corpus luteum (CL) function of mares if administered before day 5 or 6 post-ovulation. Interestingly, some of these studies reported that some mares actually responded to PGF2α -induced luteolysis when treated on day 3 post ovulation; however, the notion that the early CL was not responsive to PGF2α administration remained ingrained in the scientific and veterinary professional community. Regretfully, a plethora of research studies conducted in humans, domestic and laboratory animals have been conducted based on the premise that the developing CL does not respond to exogenous administration of PGF2α.

In 1974, Thompson and Whiterspoon briefly reported another phenomenon that has recently gained attention: the ability of PGF2α to induce partial luteolysis followed by resurgence in CL function characterized by a transient increase in concentrations of blood progesterone. In that study, two mares receiving a relatively low dose of a synthetic PGF2α analogue nine days after ovulation began to experience a decrease in concentrations of plasma progesterone at 12 h after PGF2α treatment followed by a resurgence in progesterone concentrations at 48 h after treatment; progesterone concentrations then remained at 30 to 50% of that before PGF2α treatment.

The administration of PGF2α in the periovulatory period has been used for its ecbolic effects to treat delayed uterine clearance that may lead to persistent post-mating endometritis (Troedsson et al., 2001; Nie et al., 2003). However, critical consideration of the effects of this treatment on luteal function provided some of the first evidence of luteal resurgence. In evaluating the effects of this periovulatory PGF2α treatment, the effects of administration of 500 ug of the PGF2α analog, cloprostenol, on days 0, 1, and 2 or on day 2 affected luteal function and pregnancy outcome. Both treatments had a transient negative impact on luteal steroidogenesis as determined by concentrations of plasma progesterone, and pregnancy rate was significantly lower following PGF2α treatment as compared to untreated control mares. In another report, it was found that administration of two standard (250 ug) or micro (25 ug) doses of cloprostenol on day 0, 1, or 2 resulted in decreased concentrations of plasma progesterone, slower rise in progesterone following ovulation, and a shortened interovulatory interval. However, studies from this group did not show a negative impact on pregnancy rate. Although, not initially apparent to the authors of these studies, the results highlighted the effects of early diestrus PGF2α administration, resulting in significant effect on luteal function and illustrating the phenomenon of luteal resurgence.

More recently, Bergfelt et al. (2006) compared the pattern of luteolysis following PGF2α treatment as a single bolus injection on day 3 after ovulation with that of mares treated on day 10. In the day 3 group, 75% (12/16) of mares experienced CL resurgence. Among those, six mares experiencing "minor" progesterone

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resurgence had similar treatment-to-ovulation intervals to control mares. In summary, CL resurgence following PGF2α treatment results in partial luteolysis of the CL. Partial luteolysis is evident via decreasing concentrations of blood progesterone and followed by resurgence of CL function. The resurgence is denoted by a moderate increase in progesterone concentrations. Partial luteolysis followed by CL resurgence may occur following administration of sub-luteolytic boluses doses of PGF2α during mid diestrus, or following administration of single injections at day 3 after ovulation.

PGF2α treatment and antiluteogenesis

In recent years, our laboratory has reported that luteolysis or prevention of luteal formation may be accomplished with PGF2α administration beginning as early as the day ovulation is detected (Rubio et al., 2008; Coffman et al., 2014). This effect is dependent on the dose and frequency of PGF2α treatments. Based on the fact that the early developing CL <5 days is actually responsive to luteolytic effects of PGF2α, a series of experiments conducted in our laboratory produced data that support the hypothesis that the early developing CL is indeed responsive to exogenous PGF2α as early as within the first 24 h from ovulation. Because of this early luteolytic response to PGF2α administration before the CL is fully functional, we named this phenomenon (PGF2α -induced) antiluteogenesis. Mares treated once or twice daily for three days with 2.5 or 10 mg of PGF2α dinoprost beginning at detected ovulation failed to show a significant rise in concentrations of plasma progesterone during the treatment period. Approximately 60% of mares treated twice daily for three days with 10 mg of PGF2α experienced complete antiluteogenesis where all mares receiving once daily 2.5 mg of PGF2α for three days showed CL resurgence. In a follow-up study, addition of two additional doses on days 3 and 4 following twice-daily administration resulted in an antiluteogenic response in 10 of 10 mares. There was no difference in the pregnancy rate when compared to the same mares artificially inseminated in a post-treatment cycle who were previously treated with a single injection in mid diestrus. Therefore, antiluteogenesis effect of PGF2α is dependent on the dose and frequency of PGF2α treatments.

Conclusions

Manipulation of the estrous cycle with $PGF_{2\alpha}$ is an important strategy in the breeding management of mares. The CL is sensitive to $PGF_{2\alpha}$ treatment throughout the whole estrous cycle. A single bolus injection of PGF2α can reliably induce luteolysis when administered in mares with a CL at least 5 days old. Serial injections of PGF2α for several days beginning (q 12 or q 24 h) as early as within 24 h from ovulation will prevent CL formation (antiluteogenesis) as evidenced by the absence of a sustained rise in progesterone. Not only is diestrus shortened in mares treated with PGF2α, but interovulatory intervals are also reduced in relation to normal, untreated cycles. Estrus and ovulation occurring after PGF2α treatments are normal and the inherent fertility of mares treated is not affected.

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