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Review Article

A Review on the Use of Prostaglandin $F_{2\alpha}$ for Controlling the Estrous Cycle in Mares

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ABSTRACT

Administration of exogenous prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) to induce luteolysis and return to estrus is the most commonly used method of pharmacologic manipulation of the estrous cycle in mares. The identification of $PGF_{2\alpha}$ as the endogenous luteolysin and the luteolytic effects of exogenous hormone administration were demonstrated in the 1970s. After the initial surge in research and information the physiology and pharmacology of $PGF_{2\alpha}$, there was a relative lull in investigation of the effects of $PGF_{2\alpha}$ administration on ovarian and uterine physiology. However, effects of exogenous $PGF_{2\alpha}$ administration on luteal function have received increased attention in the last decade. In particular, studies have shown various responses of the corpus luteum to different protocols (dosage, timing, frequency) of administration, including administration in early diestrus (the "refractory" period). The current review focuses on our understanding of the various responses of the corpus luteum to $PGF_{2\alpha}$, novel approaches to pharmacologically manipulate the equine estrous cycle, and potential applications in veterinary practice.

1. Introduction

Prostaglandins are modified long-chain fatty acids containing 20 carbon atoms: eicosanoid hormones. The cyclooxygenase pathway uses prostaglandin synthases to convert arachidonic acid into prostaglandins. Arachidonic acid is available through the hydrolysis of phospholipids present in the cell membrane. The breakdown of membrane phospholipids is catalyzed by the enzyme phospholipase A. Two isoforms of prostaglandin synthase exist: a constitutive (cyclooxygenase-1) and an inducible (cyclooxygenase-2) isoform. The first evidence for production of a uterine luteolysin in mares, as in other species, came from experiments demonstrating prolongation of corpus luteum (CL) function after hysterectomy [1]. It was also demonstrated the administration of exogenous prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) resulted in shortening of diestrus and return to estrus, first in rats [2] and soon thereafter in mares [3]. However, it was not until over half a decade later that the endogenous $PGF_{2\alpha}$ metabolite was first identified and measured in the uterine vein of anesthetized mares [4] and increased $PGF_{2\alpha}$ metabolite concentrations were detected concomitant with occurrence of luteolysis during the estrous cycle [5]. These experiments provided compelling evidence that $PGF_{2\alpha}$ is the luteolytic agent in mares. Because the initial evidence of the exogenous $PGF_{2\alpha}$ administration effectively induces luteolysis and return to estrus, its use has become one of the most common methods of pharmacologic manipulation of the estrous cycle in mares that is fundamental to equine reproductive practice.

Early studies estimated the equine CL has an 18-fold greater sensitivity as compared with the bovine [6,7]. Indeed, an in vitro study has shown the affinity of equine luteal cell membrane preparations for $PGF_{2\alpha}$ to be approximately 10 times greater than that for bovine luteal cell membrane preparations [8]. In addition, the plasma clearance is approximately five times lower in mares as

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compared with heifers, resulting in an approximately threefold increase in the distribution and elimination phases half-lives [9]. The relatively high affinity of mare CL to binding of $PGF_{2\alpha}$ along with the relatively slow metabolic clearance documented in mares accounts for the greater sensitivity of mare CL to the luteolytic effect of $PGF_{2\alpha}$ when compared to other domestic species.

The use of injectable preparations of $PGF_{2\alpha}$ to induce luteolysis has revolutionized the breeding management of horses and cattle. The luteal phase of the equine estrous cycle can be reliably shortened by inducing complete luteolysis with administration of $PGF_{2\alpha}$ to cycling mares [3]. A single luteolytic dose of $PGF_{2\alpha}$ administered intramuscularly or subcutaneously is sufficient to induce luteolysis if administered at least 5 days postovulation. Treated mares may return to estrus at a relatively predictable time (on average 2 to 5 days after $PGF_{2\alpha}$ administration) with ovulation occurring on average 7 to 10 days after the treatment [10]. The individual mare response is determined by follicular size and status, and the application of ultrasonography enhances the ability to predict treatment-to-ovulation intervals. Ovulation may occur as early as 48 to 72 hours after $PGF_{2\alpha}$ administration in mares with a preovulatory follicle at the end of its growing phase. On the other hand, $PGF_{2\alpha}$ treatments in the presence of a follicle undergoing atresia or a small preovulatory follicle in its initial growing stages might lead to prolonged treatment-to-ovulation intervals, some as long as 15 days [11]. In the early studies, it was recognized that luteolysis was not consistently induced with a single dose of $PGF_{2\alpha}$ in early diestrus [10]. This fact led to the prevailing assumption that the CL is not responsive to the luteolytic effects of $PGF_{2\alpha}$ before it is at least 5 day old (i.e., there is a refractory period). Curiously, in an early report, the authors did find that two of five mares underwent complete luteolysis after $PGF_{2\alpha}$ administration on day 3 after ovulation [10]. That finding, however, did not lead into further investigation on the depth of CL sensitivity to exogenous $PGF_{2\alpha}$ during the early postovulatory period.

In the United States, the natural analogue dinoprost tromethamine (Dinoprost tromethamine; Lutalyse; Pfizer Animal Health, Kalamazoo, MI) is the only $PGF_{2\alpha}$ approved by the Food and Drug Administration (FDA) agency for use in horses. Nevertheless, equine practitioners commonly use the synthetic analogue cloprostenol in breeding management, mostly owing to its presumed longer half-life than dinoprost. The objective of this review is to revisit the effects of $PGF_{2\alpha}$ on luteal function, characteristics of the induced estrus and ovulation, and clinical application including strategies for administration of $PGF_{2\alpha}$ during early diestrus. The use of $PGF_{2\alpha}$ as an abortifacient and ecbolic for breeding management will not be presented, and the reader is referred for reviews on the subject elsewhere [12–15].

2. Effects of $PGF_{2\alpha}$ Administration on the Mare's Reproductive Cycle

Natural luteolysis begins approximately 14 days after ovulation in mares. In the 1970s, several studies investigated the effects of $PGF_{2\alpha}$ treatment on blood progesterone concentration profile and effects of the length of diestrus and interovulatory intervals [3,10,16,17]. Most of these studies were based on examinations of serial blood samples taken before and after treatment with $PGF_{2\alpha}$ or based on the recording of the length of interovulatory intervals in treated and control mares. Studies on subsequent $PGF_{2\alpha}$-induced estrus, follicular dynamics, and ovulation were based mainly on findings of serial reproductive examinations using palpation per rectum. More recently, a significant wealth of information on the characteristics of luteal development and regression, follicle growth, and ovulation after $PGF_{2\alpha}$-induced luteolysis became available with the advent of transrectal ultrasonography. The information gained with ultrasonography studies on mare reproduction contributed to the understanding of exogenous $PGF_{2\alpha}$ actions on the mare's reproductive cycle and tract [18,19]. Specifically, follicular size at the time of treatment and its status (growing vs. atresia) was found to affect the treatment-to-ovulation intervals in mares (see Section 7.1).

Before $PGF_{2\alpha}$ was identified as the uterine luteolysin, it was recognized that uterine lavage with saline solution would induce a return to estrus in mares exhibiting a prolonged luteal phase in the absence of pregnancy [20–22], and this became a treatment for persistent CL function. Controlled studies demonstrated that intrauterine infusion of saline solutions 6 days postovulation shortened the estrous cycle in mares [23]. The shortened cycle was characterized by interruption of luteal activity, termination of diestrus, and return to a subsequent estrus [17].

Soon after $PGF_{2\alpha}$ was shown to be the uterine luteolysin in cattle, sheep, and rats, Douglas and Ginther published convincing evidence in 1972 that exogenous (subcutaneous or intramuscular) or intrauterine administration of $PGF_{2\alpha}$ had also luteolytic effects in mares [17]. Since then, $PGF_{2\alpha}$ and its synthetic analogues have been widely used for intensive broodmare management [19]. In the initial study by Douglas and Ginther [3], all mares treated with 1.25, 2.5, 5.0, or 10.0 mg of $PGF_{2\alpha}$ (intramuscularly) on day 6 postovulation had shorter diestrus and shorter interovulatory intervals than control mares (not treated with $PGF_{2\alpha}$). After that report, several other studies confirmed that $PGF_{2\alpha}$ treatments not only shorten diestrus but also interovulatory intervals. Despite the fact some mares may undergo complete luteolysis when treated on day 3 after ovulation, consistent luteolytic response to a single bolus intramuscular injection is expected when at least 5 days have elapsed from ovulation [10]. To avoid the risk of resurgence of the CL, the authors recommend repeating the $PGF_{2\alpha}$ treatments for a couple of days whenever ovulation dates are unknown.

3. Luteolytic Doses of $PGF_{2\alpha}$ Preparations

3.1. Dinoprost Tromethamine

Dinoprost tromethamine is the tham salt of the naturally occurring $PGF_{2\alpha}$ molecule and remains the only product labeled for use in mares in the United States. Comparing the salt with free acid $PGF_{2\alpha}$, 1.34 mg is the equivalent 1 mg of $PGF_{2\alpha}$. Douglas and Ginther [3] reported that doses of 1.25, 2.5, 5.0, and 10.0 mg of $PGF_{2\alpha}$ (free acid) administered intramuscularly. were all found to shorten