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Opinions and Hypotheses

Clinical prospects proposing an increase in the luteolytic dose of prostaglandin $F_{2\alpha}$ in dairy cattle

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Abstract. Over the past few decades, the luteolytic dose of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and its analogs, used to synchronize estrus for fixed-time insemination in dairy cattle, have remained unchanged. Given the beneficial effects of $PGF_{2\alpha}$ on a young corpus luteum and on multiple ovulations in a fixed-time insemination protocol, and its therapeutic abortive effects on multiple ovulations in pregnant cows, we propose the use of a double $PGF_{2\alpha}$ dose or two $PGF_{2\alpha}$ treatments 24 hours apart. Ultrasonography procedures serve to identify luteal structures and may therefore help to determine the best $PGF_{2\alpha}$ dose to improve the fertility of high-producing dairy cows.
Key words: Additional corpora lutea, Cloprostenol, Double ovulation, Fixed-time artificial insemination (FTAI), Twin pregnancy

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Introduction

In the 1970s, there were extensive reports of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and its analogues being luteolytic in cattle, with the degree of fertility of the induced estrus similar to that achieved in previous studies [1, 2] or higher than that of naturally occurring estrus [3]. Traditionally, the use of these substances was based on shortening the luteal phase. This meant that a treatment was only effective in the presence of a functional corpus luteum (CL), and if done within 5–16 days of a normal estrous cycle [4], which is approximately 60% of a population cycling at random. The dose-response effect for luteolytic agents synchronizing estrus was also established in the 1970s: $PGF_{2\alpha}$, 25 mg; cloprostenol, 500 µg; and fenprostalene, 1 mg [1, 2]. These luteolytic doses remained unchanged with the development of different estrus synchronization protocols within the last 50 years of dairy cattle rearing. This would appear to mean that the success of treatment with luteolytic products has reached a plateau. However, higher metabolic clearance rates of steroid hormones and alterations in reproductive endocrinology have been linked to the process of high milk production [5–7]. Consequently, exogenous prostaglandins are likely to be exposed to a rapid metabolism or a less significant response excluding increased milk production. In fact, although endogenous $PGF_{2\alpha}$ entering the pulmonary circulation is enzymatically inactivated in the lungs [8], biliary excretion is a major route of elimination of cloprostenol [9]. The question therefore arises as to whether one should accept current levels of success or, alternately, introduce new findings leading to the modification of prostaglandin dose. Moreover, while an important body of literature shows that the recommended $PGF_{2\alpha}$ dose is still sufficient, some clinical reflections based on our experimental studies and extensive field-scale experience are provided to: 1) emphasize the features of current synchronization protocols for fixed-time artificial insemination (FTAI), 2) highlight the challenge of multiple ovulations associated with high milk production, and 3) improve the control of pregnancies.

Breeding synchronization protocols in dairy herds

Increased herd size combined with intensive milking and feeding, poor detection of estrus, and increased post-partum anestrus, make individual animal monitoring very difficult. These are cogent reasons why breeding synchronization protocols for FTAI have become routine components of the reproductive management of dairy herds. For example, the $PGF_{2\alpha}$-based ovulation synchronization protocol, denoted "Ovsynch," is extensively applied for FTAI of lactating dairy cows [10, 11]. The Ovsynch method consists of a gonadotrophin-releasing hormone (GnRH) treatment given at random stages of the estrous cycle (to synchronize a follicular wave), followed by $PGF_{2\alpha}$ seven days later (to stimulate the luteolytic effect on a CL). A second dose of GnRH is administered 36–48 h after $PGF_{2\alpha}$ treatment (in order to synchronize ovulation) and the cows are inseminated 16–20 h later without detection of estrus [10, 11]. However, about 60% of cows ovulate after the first GnRH treatment and form a new CL so that the CL age at $PGF_{2\alpha}$ treatment is about 5–6 days [12]. This is why incomplete

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luteal regression after treatment, with a single dose of $PGF_{2\alpha}$, during an Ovsynch protocol decreases fertility. Another reason for the insufficient results of the Ovsynch protocol is that it should not begin at random stages of the estrous cycle. For example, Ovsynch applied in the last third of the estrous cycle is not sufficient to ensure synchronization of estrus and ovulation in each animal treated [13].

A meta-analytical assessment was recently performed with the objective of evaluating the effects of adding a second $PGF_{2\alpha}$ treatment 24 h after the first, during the Ovsynch protocol, on luteal regression and reproductive performance in lactating dairy cows [14]. An additional $PGF_{2\alpha}$ treatment yielded an increase of 11.6% on luteal regression and 4.6% on pregnancies per insemination [14]. The fact that 1.5 [15] or 2 [16] doses of d-cloprostenol favored luteolysis when administered to cows with a 5- to 6-day-old CL, reinforces these results. Furthermore, a double dose of $PGF_{2\alpha}$ administered 3.5 days post-ovulation resulted in partial luteolysis in 78% of treated animals, and full luteolysis in the remaining 22% [17]. In the latter study, partial luteolysis occurred when the progesterone concentration decreased by 12 h of treatment and finally increased to values similar to that of untreated controls during the luteal phase. Whereas, full luteolysis occurred when the progesterone concentration decreased below 1 ng/ml within 48 h of treatment and remained < 1 ng/ml until a new ovulation cycle [17]. As noted above, the threshold age for a responsive CL was set at five days [4]. However, with regards to a repeated administration of $PGF_{2\alpha}$, the second dose may just overcome the time problem of a refractory CL instead of dose dependence.

Research continues on methods of synchronization, and opinions vary on the best method available. Five-day P4-based protocols with either two $PGF_{2\alpha}$ treatments 24 hours apart [18–21], or a double dose of $PGF_{2\alpha}$ [20], have provided results that compare favorably with those observed for longer protocols. Therefore, an increased dose of $PGF_{2\alpha}$, or a second treatment with $PGF_{2\alpha}$ 24 h after the first, should be recommended in FTAI protocols.

Control of pregnancy

Therapeutic abortion may be required during normal pregnancies (accidental breeding of a very young heifer) or abnormal pregnancies (fetal mummification, hydramnios, or hydro-allantois). It should be noted here that there also exists the problem of multiple ovulations. The significance of the double ovulation effect in high producers at insemination may be over 20% [21–25]. Because double ovulation has been linked to higher fertility [22, 26]; once a cow is pregnant the percentage of cows with two or more CL should be higher. In effect, in a recent study on 2173 pregnant cows in their third lactation or more [27], 1119 (51.5%) had at least two CL: 422 (19.4%) carrying singletons and 697 (32.1%) carrying twins. Twin pregnancies are not desirable for the economy of dairy cattle. With an economic burden estimated up to $225 per pregnancy in the U.S.A., the use of $PGF_{2\alpha}$ for inducing abortion may be a suitable option upon a diagnosis of twins [28].

The CL of pregnancy appears essential for maintaining pregnancy prior to 165 days of gestation [29] and a single $PGF_{2\alpha}$ treatment consistently induces abortion until approximately 150 days of gestation, generally without complications [30]. However, a double $PGF_{2\alpha}$ dose between days 40 and 120 of gestation resulted in abortion of all treated cows, in contrast to a single or lower dose, which were either less effective or totally ineffective [31]. In the latter study, only one single CL was present for each pregnancy, suggesting that a double dose is better than a single $PGF_{2\alpha}$ dose for terminating pregnancy. It is likely that a double dose of $PGF_{2\alpha}$ is sufficient to induce abortion in cows with two CL. However, future studies should assess this assertion or establish a dose-response protocol in double-ovulating pregnant cows. In pregnancies in which the number of CL exceeds the number of embryos, this additional CL has proven to be a very strong factor favoring pregnancy maintenance [32].

Concluding remarks

The decline in the reproductive performance of high-producing dairy cows has been observed in the last few decades. This decline has been partly related to the high metabolism of steroid hormones and subsequent alterations to reproductive endocrinology, which is linked to increased milk production. Under these circumstances, $PGF_{2\alpha}$-based FTAI protocols have become increasingly common. However, up to 60% of cows have a young CL while undergoing $PGF_{2\alpha}$ treatment, thereby reducing fertility. Furthermore, the number of cows with two or more CLs that are beginning treatment according to FTAI protocols is increasing, as is the case for pregnant cows. Consequently, the impact of multiple CLs reinforces the idea of a growing need to increase the luteolytic dose. There are dose-dependent studies showing that a lower dose of $PGF_{2\alpha}$ still works within FTAI protocols [15] or on pregnant cows [33]. However, we concur that the treatment of two $PGF_{2\alpha}$ treatments administered 24 hours apart in the FTAI protocols, or a double dose of $PGF_{2\alpha}$ given to cows with a young CL and to pregnant cows for therapeutic abortion, should be recommended. Furthermore, ultrasonography procedures may help in identifying luteal structures, thereby deciding the $PGF_{2\alpha}$ dose and improving the results in high-producing dairy cows.

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