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Effect of PRID administration post-insemination on the establishment of pregnancy of dairy cows under commercial farm conditions

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ABSTRACT. The aim of this study was to test the efficiency of progesterone supplementation post insemination (p.i.) in the fertility of dairy cows under commercial farm conditions. At initiation of the study, 405 cows from three farms -irrespective of their open days- were bred after natural or synchronized estrus. Subsequently, the cows were randomly allocated to receive a progesterone-releasing intra-vaginal device (PRID®) between D5 and D17 p.i (P4+, n=213), or to remain untreated (P4-, n=192). Pregnancy per artificial insemination (P/AI) did not differ between P4+ (42.3%) and P4- (41.2%, P = 0.82) groups. However, the treatment improved P/AI in cows enrolled in the study after the second p.p. insemination (46.8 vs. 25.5, P = 0.02). In the farm that showed the less days to insemination before treatment, progesterone supplementation tended to raise the P/AI (48.2 vs. 23.5, P = 0.08). However, in the farm with the greatest fertility the P4+ group had significantly lower P/AI than the P4- group (37.7 vs. 57.4, P = 0.03). Conclusively, the beneficial effect of the post-insemination administration of PRID is mainly apparent only after the second p.p. insemination and probably during early lactation when fertility is suppressed.

Keywords: dairy; cow; fertility; progesterone supplementation

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INTRODUCTION

Early and late embryonic mortality is considered a common problem of high yielding dairy cattle and can lead to poor reproductive performance (Bilodeau-Goeseels & Kastelic 2003; Lopez-Gatius 2012). Progesterone (P4) during the early stages of gestation plays a key role in embryo survival. It facilitates and sustains a uterine environment, which is friendly for embryo growth, implantation and development (Green et al. 2005; Forde et al. 2009; Mullen et al. 2012). Elevated concentrations of progesterone have been associated with increased pregnancy retention during early gestation (Starbuck et al. 2004). However, according to Stronge et al. (2005) almost 75% of modern dairy cows will suffer from sub-optimal P4 concentrations during the early luteal stage. Dairy cows that have low concentrations of progesterone may have a higher metabolic clearance rate of P4 in the liver due to a higher dry matter intake and a higher liver blood flow (Wiltbank et al. 2006; Lemley et al. 2008). Moreover, low concentrations of progesterone after insemination has been implicated in the pathogenesis of repeat breeding and poor reproductive performance (Ferguson et al. 2012). Research has been directed towards the development of different hormonal treatments during early pregnancy that could enhance embryo survival. Administration of GnRH (Franco et al. 2006), hCG (Torres et al. 2013), or progestagen releasing intravaginal devices (PRID®, CIDR®) (Lopez-Gatius et al. 2004; Forro et al. 2012) seem to contribute to P4 concentration and consequently, facilitate embryonic survival. CIDR® or PRID® are usually placed 4-5 days post insemination (p.i) (Yan et al. 2015) and remain in situ until 17-18 day p.i. (Forro et al. 2012). However, P4 supplementation can have both embryotrophic and luteolytic effects (O'Hara et al. 2014). PRID® administration before D5 seems to have a negative effect on CL development, as it inhibits LH secretion (Mann et al. 2006; O'Hara et al. 2014). Additionally, it has been reported that the administration of P4 as early as D1-D3 of the estrus cycle, could lead to an earlier return to estrus (O'Hara et al. 2014).

The beneficial effects of such treatments have to be cost effective and relevant to the everyday farm conditions. P4 supplementation with PRID® or CIDR® alone between D5 to D18 in order to improve pregnancy rates has been previously tested with beneficial (Larson et al. 2007; Forro et al. 2012) or inconsistent results (Villarroel et al. 2004; Stevenson et al. 2007). Based on a recent meta-analysis from Yan et al. (2015), there are conditional effects instead of an overall positive effect from progesterone supplementation p.i. Specifically, it seems that the administration of progesterone post insemination had a positive effect only in cows of lower fertility and after natural estrus (Yan et al. 2015).

We hypothesized that the administration of a progesterone-releasing intra-vaginal device between Day 5 and Day 17 after insemination would improve pregnancy per AI (P/AI). The overall purpose of the study was to investigate the amplitude and consistency of this benefit under commercial farm conditions.

MATERIALS AND METHODS

2.1. Animals, experimental design and treatment

This study was performed on three commercial dairy farms of approximately 100, 120 and 150 mature lactating dairy cows in central and north Greece over an approximately 2-year period. Mean annual milk production of the herds for this period ranged from 9,800 to 10,500 kg per cow. The cows were milked three times daily and were housed in freestall barns.

The health status of all cows was assessed during the first 3 days after parturition. Moreover, the reproductive management of farms included a routine examination of the reproductive tract of the cows to monitor uterus involution and ovarian activity within four weeks after parturition. Any detected clinical abnormality was treated according to health protocols and only cows without abnormal vaginal discharge were subjected to artificial insemination (AI). The voluntary waiting period (VWP) in the three farms ranged between 55 and 65 days in milk (DIM). Artificial insemination was performed by the owner of each farm and according to farm's previous data the effectiveness in all three farms was similar. At initiation of the study, not pregnant cows -irrespective of their open days-showing estrus (in all three farms cows were observed twice daily, for estrus detection) during the first fifteen days were inseminated following the am-pm rule. The remaining cows were examined and, a) in the case of absence of a CL, were enrolled into the Ovsynch protocol (Pursley et al. 1995) followed by timed artificial insemination (TAI) or b) if a CL was palpated, were injected with PGF2α and were inseminated after heat detection. In case of estrus absence 5 days after the PGF2α administration animals were also enrolled into the Ovsynch protocol. The commercially available frozen semen used for the insemination was of proven fertility. Following the insemination, the cows of the three farms were randomly allocated to receive a progesterone-releasing intra-vaginal device (PRID®, containing 1.55g of progesterone, CEVA) on D5 post insemination and remove it on Day 17 (P4+ group, n=213), or to remain untreated (P4- group, n=192). In every cow PRID® was applied only once. Pregnancy check was performed by transrectal palpation at a time point between 38 and 45 days p.i. and confirmed at 68-75 days p.i.

2.2. Statistical analysis

Statistical analysis was conducted using the Statistical Analysis System V9.3 (SAS Institute Inc., Cary, NC, USA). The Shapiro–Wilk test was performed in all outcome variables to test for the underlying distribution of the data. In order to detect differences between farms regarding productive and reproductive parameters Kruskal-Wallis one way ANOVA and Wilcoxon's two sample test were applied. Where univariate analysis was used, differences in binary variables were evaluated with the use of chi-squared analysis. For the effect on pregnancy, analysis was run by the application of a linear logistic model with a binary response variable (Proc GLIMMIX). A set of variables were used in the statistical model for their effect on pregnancy, namely number of inseminations that the cow had received (1, 2, 3, 4, greater than 4), days to insemination (up to 80, between 81 and 200, greater than 200 days), milk yield on the day of the insemination divided in 4 equal quartiles (<24kg, 24-<31kg, 31-<36kg and greater or equal to 36kg), parity (first, second, third, greater or equal to forth), season (summer, from April to September, vs. winter), and progesterone supplementation (yes vs. no). Herd was included in the model as a random effect. Effects with P-values >0.15 were removed in a stepwise backward elimination process. Progesterone supplementation was forced in all models and all two way interactions between the above mentioned parameters and PRID were tested. All analyses were considered to be statistically significant at $P < 0.05$. Quantitative data are presented as the mean ± SEM.

RESULTS

The average daily milk yield on the day of the insemination was 29.7 ± 9 kg. The average lactation number, days to insemination and number of inseminations were 2.3 ± 1.4, 192 ± 121 and 2.5 ± 1.8, respectively. However, there were significant differences between the 3 farms (Table 1). Specifically, the first farm had the lowest daily milk yield and the greatest number of inseminations, as animals of higher parity animals compared to the other two farms. On the other hand, the third farm had the greatest milk yield and the lowest days to insemination. The second farm had better P/AI than the third farm (48.1 vs. 34.2, $P = 0.05$).

Cows that received the progesterone supplementation after the second p.p. insemination showed improved P/AI compared to the untreated group (46.8 vs. 25.5, $P = 0.02$, Fig 1a). There was no significant effect from P4 supplementation in any other level of this variable. In cows with less than 80 days open the P4+ group had numerically higher P/AI compared to the P4- group (41.4 vs. 25.7, respectively, $P = 0.18$, Fig 1b). There was no significant effect from P4 supplementation in any level of milk yield, parity or season (Fig 1c, 1d, 1f). In the third farm progesterone supplementation tended to raise the P/AI (48.2 vs. 23.5, $P = 0.08$, Fig 1e). However, in the second farm the P4+ group had lower P/AI than the P4- group (37.7 vs. 57.4, $P = 0.03$, Fig 1e).

In the final model, there was no effect of open days, daily milk yield, parity, season and PRID on P/AI. However, there was a significant effect of number of insemination on P/AI ($P = 0.02$), as there was a gradual increase on the P/AI from the first to the fourth insemination (Fig 1a). Moreover, the interaction be-

Table 1: Production and reproductive data of the 3 farms (Mean ± SD)

Item	Farm 1	Farm 2	Farm 3
n	200	129	76
Parity	2.6 ± 1.5^{a}	2.0 ± 1.0^{b}	2.1 ± 1.1^{b}
Milk yield	25.5 ± 8.4^{a}	32.5 ± 7.6^{b}	36.3 ± 7.6^{c}
Days to insemination	202 ± 126^{a}	207 ± 127^{a}	138 ± 72^{b}
No. of inseminations	2.9 ± 2.0^{a}	2.3 ± 1.6^{b}	2.1 ± 1.4^{b}

Within rows, values with different superscripts differ ($P < 0.05$)

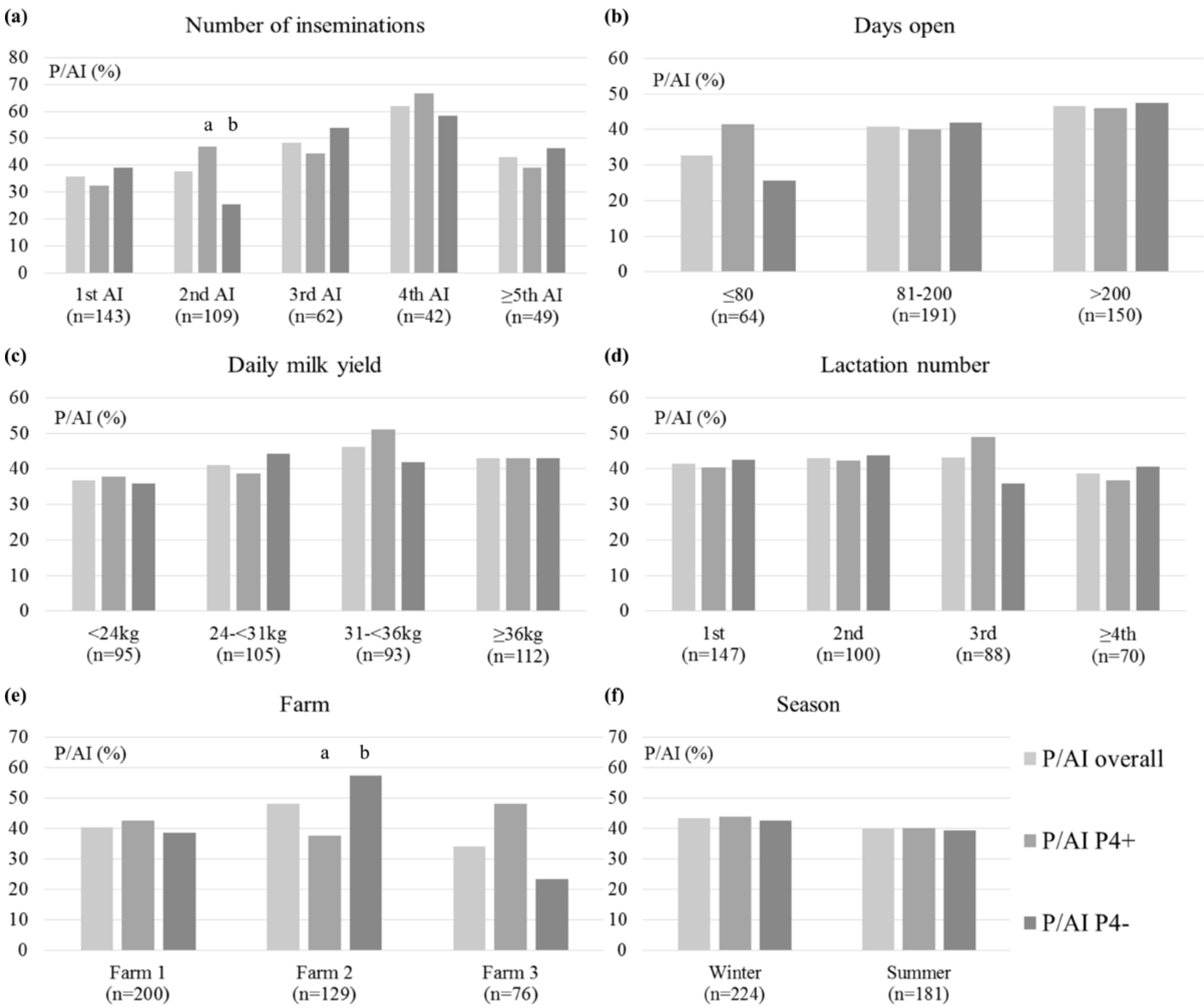

Figure 1. Effect of progesterone (P4) supplementation on pregnancy per AI (P/AI) of Holstein Friesian cows under different number of insemination (a), open days (b), daily milk yield (c), parity (d), farm (e) and season (f) levels. Values within category and level with different superscript differ ($P < 0.05$).

tween the number of insemination and PRID satisfied the cut off level for entry in the final model ($P = 0.15$).

DISCUSSION

The need of adequate progesterone levels post insemination on embryo development and survival has led to the implementation of protocols that supplement P4 post insemination in everyday farm practice. However, the response to such protocols varies widely. To our knowledge this is the first study that estimated the effect of such an intervention under commercial farm conditions.

According to Wiltbank et al. (2014) higher milk yields can lead to decreased circulating P4 concentrations due to increased feed intake and higher P4 metabolism. However, the results from the present study indicate that under farm conditions no decision for the selective PRID administration can be made based on daily milk production data. This leads to the indirect inference that PRID supplementation for the increase of pregnancy rate is not directly influenced by milk production. High milk production and negative energy balance (NEB) are reported to have a key role in embryo survival (Santos et al. 2009; Senosy et al. 2012). This effect is both direct and indirect and although NEB is noticed during the first weeks postpartum, its consequences seem to have a carryover effect on ovary activity (Roth et al. 2001; Butler 2003). Follicles containing oocytes available for fertilization have initiated their differentiation 60-80 days before estrus (Leroy et al. 2008) and it was postulated that NEB affects the steroidogenic capacity of follicles. Under such circumstances their ability for survival is diminished. Nevertheless, results from a recent research indicate that high-producing cows can still have high reproductive performance providing a successful adaptation to lactation due to effective nutritional management (Drackley & Cardoso 2014).

It has been previously reported that several environmental conditions may be associated with low plasma progesterone concentrations. Heat stress is one factor recognized as a cause of low fertility but the mechanism of action remains obscure. The role of summer in progesterone insufficiency has been reported and could be one possible mode of action (Howell et al. 1994; Sartori et al. 2002). On the other hand, it has recently been reported that repeat-breeder cows have low fertility during summer and this is related to a low oocyte competence to develop into blastocysts (Ferreira et al. 2011). This is in accordance to our findings, since the potential beneficial effect of PRID administration is expressed after blastocyst formation. In addition, it seems possible that despite the hot summer conditions in the region, the microenvironment of the farms was sufficiently supported (fans and sprinkles) to overcome any possible detrimental effect of heat stress on progesterone concentration.

Based on our results, the effect from progesterone supplementation p.i. varies from farm to farm and is diverse depending on insemination number and open days level. The animals of the farm with the smaller calving-to-PRID administration interval and, most importantly, the worst P/AI in the control group profited more from P4 supplementation compared to the other two farms. This finding implies that farms with more fragile fertility could benefit more from such an intervention. On cow level, the positive effect from P4 supplementation was evident in the second insemination and numerically in cows that were early (<80 days) in lactation, although the latter difference was not significant ($P = 0.18$). These cows had also the poorest fertility in the control group and were at greater risk for negative energy balance. Under commercial farm practices synchronization protocols are implemented later in lactation. These findings are in accordance with those of Yan et al. (2015) that reported a positive effect from P4 supplementation only in cows with low fertility and after natural estrus. On the other hand, it is difficult to explain the apparent negative effect noticed in the second farm. Yan et al. (2015) reported very wide variations across studies (-40% to +50% change) that supplemented P4 post insemination. Additionally, Yan et al. (2015) actually found a significant fall in the pregnancy rate of farms with high fertility after P4 supplementation. Nevertheless, it is more likely that there was an unexplained exceptional P/AI of almost 60% in the control group rather than a true negative effect in the treatment group that showed P/AI of almost 40%.

Conclusively, our results suggest that progesterone supplementation post insemination can improve the pregnancy rates of cows and farms at risk for low fertility. Well managed farms or cows after the period of negative energy balance are not expected to profit from such an intervention.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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