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Pathways of the dominant follicle after exposure to sub-luteal circulating progesterone concentrations are different in lactating dairy cows versus non-lactating heifers

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ABSTRACT

With the increased use of different synchronization programs in cattle, attention is given to the progesterone concentration during development of the ovulatory follicle. It has been shown that low peripheral progesterone concentrations during follicular development may lead to decreased fertility. To investigate the effect of low progesterone concentrations on the fate of the dominant follicle, a study was conducted where cycles of dairy cows and heifers were manipulated to induce the development of the first dominant follicle without progesterone (PLACEBO) or under sub-luteal progesterone concentrations from a progesterone releasing intravaginal device (PRID Delta®). After insertion of the devices, daily follow up was performed by transrectal ultrasonography to identify and measure follicular development and blood samples were taken to determine the circulating progesterone concentration. Follow up was continued until the ovulation of a follicle occurred. After ovulation, the fate of the first dominant follicle was identified as arrested, atretic or ovulatory. Arrest was defined as persistence of the dominant follicle followed by ovulation whereas atresia was defined as regression of the dominant follicle and subsequent growth and ovulation of a new follicle. During PLACEBO treatment, heifers ovulated earlier and smaller follicles in comparison to cows. During PRID Delta® treatment, heifers had greater progesterone concentrations compared to cows and arrest of the dominant follicle occurred more in cows in comparison to heifers. In cycles where the dominant follicle was arrested, the ovulatory follicle was larger in comparison to cycles where the dominant follicle was atretic.

1. Introduction

Synchronization of the estrous cycle in cattle is currently an important tool for reproductive management in both beef and dairy herds. Most of the synchronization protocols employ combinations of treatments with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), GnRH and progesterone to regress the corpus luteum in cyclic cows, to promote follicular growth and ovulation in anestrous cows, and to control follicular wave development (Lima et al., 2009; Cerri et al., 2009a), and thereby synchronizing estrus and ovulation at the end of treatment (Lucy et al., 2004). By using exogenous progesterone (P4) in combination with $PGF_{2\alpha}$, estrus response is

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relatively high, and more than 70% of the cows that come into estrus, do so between 2 and 4 days after removal of the insert (Chebel et al., 2006).

Presence of an intravaginal P4-device gives rise to sub-luteal peripheral P4-concentrations (2–4 ng/mL; Flock et al., 2010). Some studies demonstrated that at the time of luteolysis and final maturation of the dominant follicle, these sub-luteal P4-concentrations can either sustain growth of the dominant follicle leading to the formation of 'the persistent follicle phenomenon' (PFP, Bridges and Fortune, 2003), or block follicular growth resulting in atresia of the dominant follicle and emergence of a new follicular wave leading to maturation and ovulation of a 'fresh' dominant follicle (Smith and Stevenson, 1995). In all of these studies, it was assumed that the major contributors underlining these inconsistent follicular turnovers were different LH pulse frequencies (Stevenson et al., 2006; Denicol et al., 2012). Lower peripheral P4-concentrations are associated with greater LH-pulse frequencies leading to prolonged sustainment and persistence or arrest of the dominant follicle (Kinder et al., 1996). Formation of PFP extends follicular dominance (Hatler et al., 2008), which might result in premature activation of the oocyte (Mihm et al., 1999), and subsequently compromise the early stages of embryo development (Cerri et al., 2009a), leading to reduced calving rates.

Lactating cows in comparison to non-lactating heifers have two-fold lower peripheral estadiol and progesterone concentrations (Wiltbank et al., 2006), due to a significantly greater blood flow to the liver and a concomitantly increased steroid metabolization (Sangsritavong et al., 2002). Dissimilarities in the peripheral steroid hormone concentrations (especially in animals not bearing a CL) are important as they may significantly affect the effectiveness of the P4-supplementation, regarding the resulting P4-concentration in plasma which might be insufficient to optimize follicular growth and ovulation (Bisinotto and Santos, 2012).

Based on these considerations, the current experiment was designed to test the hypothesis that the fate of the dominant follicle, in particular ovulation, atresia or arrest, at the moment of luteolysis in lactating dairy cows and non-lactating dairy heifers can be influenced by the application of an intravaginal P4-device (PRID Delta®). Furthermore, we aimed to detect other factors that are significantly associated with the final fate of the dominant follicle under the circumstances of sub-luteal peripheral progesterone concentrations.

2. Materials and methods

2.1. Selection of the animals

A study was conducted including 11 lactating dairy cows and 10 non-lactating dairy heifers of the Holstein Friesian breed housed at the research dairy farm of Ghent University (Biocentrum Agri-Vet). Only healthy, cycling animals (animals bearing an active CL on one of the ovaries) were enrolled in the study. Cows were included from 35 days in milk and heifers were included from 14 months of age. Cows were housed in a loose cubicle stable, milked by an automated milking system (VMS, Delaval) and fed ad libitium a partial mixed ration while offered concentrates in the VMS and an automated feed dispenser. Heifers were housed in a loose cubicle stable and fed corn and grass silage. The experiment was approved by the Ethical Committee of the Faculty of Veterinary Medicine (EC 2010/150, Ghent University).

2.2. Experimental design

A graphical presentation of the protocol is given in Fig. 1. All animals were pre-synchronised using two injections of 25 mg Dinoprost trometamol (5 ml Enzaprost®, CEVA Santé Animale, France) administered with an interval of 14 days, after which they were closely monitored for expression of heat symptoms by the herd personnel and by daily transrectal ultrasonographic examination of the ovaries until confirmed ovulation (defined as the disappearance of the dominant follicle between two consecutive ultrasound examinations). At the initiation of the experiment, animals were randomly assigned to receive a PRID Delta® or a PLACEBO treatment. Starting from d 6 (heifers) or d 7 (cows) postestrus (day 0 = estrus), animals were monitored on a daily basis by transrectal ultrasonography and blood collection. Different days in heifers and cows were chosen as it was reported that in heifers the dominant follicle from the first follicular wave reaches the plateau period on d 7 of the estrous cycle whereas in cows the same event occurs 2 days later (Savio et al., 1990). On d 7 (heifers) or d 8 (cows) postestrus, when the dominant follicle (defined as a follicle $\geq$8.5 mm in diameter and exceeding the size of other follicles) of the first follicular wave was detected, a PRID Delta® (intra-vaginal device impregnated with 1.55 g of progesterone, CEVA Santé Animale, France) or a PLACEBO (identical intra-vaginal device without progesterone) was inserted followed by an intramuscular injection of 25 mg Dinoprost trometamine (5 ml Enzaprost®, CEVA Santé Animale, France) 24 h later. At d 13 (heifers) or d 14 (cows), animals in the PRID Delta® group received another $PGF_{2\alpha}$ injection while animals in the PLACEBO group were injected with physiological saline. The PRID Delta® and PLACEBO devices were removed 7 days after insertion (d 14 in heifers and d 15 in cows). Daily monitoring in the PLACEBO group stopped on d 14 (heifers) or d 15 (cows) while in the PRID group, monitoring continued until ovulation. After a wash out period of 7 days, the protocol was repeated where the PRID Delta® group became the PLACEBO group and vice versa. At the beginning of each treatment, age (heifers) or DIM (cows) was recorded and the BCS of each animal was assigned using a scale from one to five (Edmonson et al., 1989). Daily milk production of the cows during the treatment was calculated based on the milk recordings in the VMS.

2.3. Ovarian ultrasonography

Monitoring of follicular dynamics was done by transrectal ultrasonography of the ovaries using a portable ultrasound machine equipped with a linear 7.5 MHz transducer (Tringa®, Esaote, The Netherlands). Ovarian maps were drawn for each cow on each day to record size and