



Carryover effect of postpartum inflammatory diseases on developmental biology and fertility in lactating dairy cows

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ABSTRACT

The objective of this series of studies was to investigate the effects of inflammatory diseases occurring before breeding on the developmental biology and reproductive responses in dairy cows. Data from 5 studies were used to investigate different questions associating health status before breeding and reproductive responses. Health information for all studies was composed of the incidence of retained fetal membranes, metritis, mastitis, lameness, and respiratory and digestive problems from parturition until the day of breeding. Retained placenta and metritis were grouped as uterine disease (UTD). Mastitis, lameness, digestive and respiratory problems were grouped as nonuterine diseases (NUTD). Study 1 evaluated the effect of disease before artificial insemination (AI), anovulation before synchronization of the estrous cycle, and low body condition score at AI on pregnancy per AI, as well as their potential interactions or additive effects. Study 2 investigated the effect of site of inflammation (UTD vs. NUTD) and time of occurrence relative to preantral or antral stages of ovulatory follicle development, and the effect of UTD and NUTD on fertility responses of cows bred by AI or by embryo transfer. Study 3 evaluated the effect of disease on fertilization and embryonic development to the morula stage. Study 4 evaluated the effect of disease on preimplantation conceptus development as well as secretion of IFN- τ and transcriptome. Study 5 investigated the effect of diseases before AI on the transcript expression of interferon-stimulated genes in peripheral blood leukocytes during peri-implantation stages of conceptus development after first

AI postpartum. Altogether, these studies demonstrated that inflammatory disease before breeding reduced fertilization of oocytes and development to morula, and impaired early conceptus development to elongation stages and secretion of IFN- τ in the uterine lumen. Diseases caused inflammation-like changes in transcriptome of conceptus cells, increased risk of pregnancy loss, and reduced pregnancy or calving per breeding. Moreover, the effects on reproduction were independent of cyclic status before synchronization of the estrous cycle and body condition score at breeding, which all had additive negative effects on fertility of dairy cows. Occurrence of disease at preantral or at antral stages of ovulatory follicle development had similar detrimental effects on pregnancy results. The carryover effects of diseases on developmental biology might last longer than 4 mo. Reduced oocyte competence is a likely reason for carryover effects of diseases on developmental biology, but impaired uterine environment was also shown to be involved.

Key words: dairy cow, disease, embryo, fertility

INTRODUCTION

Transition from the nonlactating pregnant state to nonpregnant lactating state requires a dairy cow to drastically adjust her metabolism so that nutrients can be partitioned to support milk synthesis, a process referred to as homeorhesis (Bauman and Currie, 1980). A sharp increase in nutrient requirements generally occurs at the onset of lactation, when feed intake is usually depressed, which causes extensive mobilization of body tissues, particularly body fat, but also AA, minerals, and vitamins (Santos et al., 2010). Despite orchestrated homeostatic controls and homeorhetic adjustments to cope with the changes in metabolism caused by milk production, 40 to 70% of dairy cows across different levels of milk production, breeds, and management systems develop metabolic or infectious diseases in the first months of lactation (Santos et al., 2010; Ribeiro et al., 2013). These health problems not

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only cause reductions in milk production and increases in production costs, but also reduce reproductive performance of dairy cows (Santos et al., 2010; Ribeiro et al., 2013), which consequently impairs sustainability of dairy herds (Ribeiro et al., 2012).

Reproductive efficiency in dairy herds depends on adequate submission of lactating cows to breeding in a timely manner with adequate pregnancy per AI (P/AI). The development of programs that efficiently synchronize the estrous cycle and ovulation of cattle and the current increase of their usage for management of reproduction of dairy herds have successfully improved submission to insemination (Bisinotto et al., 2014); nonetheless, the resulting P/AI still is suboptimal. Early embryonic mortality in lactating dairy cows is substantial (Santos et al., 2004; Diskin et al., 2006) and likely the main cause of inadequate pregnancy results. Interestingly, early pregnancy losses do not seem to occur randomly, but have predisposing factors. Inflammatory diseases occurring before breeding (Santos et al. 2010; Ribeiro et al., 2013), anovulation before synchronization of the estrous cycle (Santos et al., 2004), and low BCS at AI (Santos et al., 2009) are factors that have been implicated with reduced P/AI and increased early and late embryonic mortality. Diseases have great significance for reproduction in dairy herds because of the high prevalence and because of the association with other fertility stressors such as anovulation and low BCS (Santos et al., 2009; Santos et al., 2010; Ribeiro et al., 2013).

The biological mechanisms by which postpartum diseases impair reproduction, however, are not clearly understood. Most studies are of an epidemiological nature and the overwhelming majority associate negative effects of diseases during early lactation with reduced P/AI or extended intervals to pregnancy. Important questions remain on how diseases affect developmental biology, whether diseases that are of uterine or non-uterine origin affect fertility differently, the timing of disease occurrence relative to breeding, and the role of other associated risk factors that depress fertility, such as anovulation and low BCS, that are more prevalent in cows that suffer disease. Altogether, the biology that underlies subfertility attributed to diseases remains elusive and deserves investigation.

The objectives of this series of studies were to characterize the effect of inflammatory diseases before breeding on developmental biology and reproduction in dairy cows. To accomplish the objectives, we attempted to (1) isolate the effects of diseases, anovulation at the initiation of synchronization program, and low BCS at breeding and their potential interactions or additive effects; (2) isolate the effects of uterine and nonuterine diseases and their potential interactions or

additive effects; (3) evaluate the importance of the time when the disease occurs relative to breeding regarding effects on reproduction, as well as the contribution of the uterine environment during posthatching stages of embryo development on the etiology of subfertility caused by diseases before breeding; (4) evaluate the effect of disease on fertilization and embryonic development to the morula stage and the effect of disease on preimplantation conceptus development as well as secretion of IFN- τ and transcriptome; and (5) evaluate the effect of diseases before AI on the transcript expression of interferon-stimulated genes in peripheral blood leukocytes during peri-implantation stages of conceptus development.

MATERIALS AND METHODS

Study 1: Disease, Anovulation, and Low BCS and Effects on Fertility Responses

The objective of study 1 was to evaluate the effect of inflammatory diseases before AI, anovulation before synchronization of the estrous cycle, and low BCS at AI on P/AI for the first AI postpartum, as well as their potential interaction or additive effects. The 3 traits have often been implicated individually with reduced fertility in dairy cows, and only a few studies have investigated the relationship or dependence among them (Hernandez et al., 2012; Vieira-Neto et al., 2014). For that, information regarding health of cows from parturition to first AI, estrous cyclicity before estrous cycle synchronization, BCS at AI, and P/AI at first AI postpartum was evaluated from 2,190 cows enrolled in 5 controlled experiments: 4 conducted in Florida (Lima et al., 2014; Ribeiro et al., 2013; 2015; Wang et al., 2013) and 1 in California (Rutigliano et al., 2008).

Retention of fetal membranes was recorded on the first day postpartum and cows were evaluated for the incidence of metritis by transrectal palpation and examination of uterine discharge on the first 10 d postpartum. Incidence of mastitis, lameness, and digestive and respiratory problems were evaluated from parturition until first AI postpartum. At every milking, all cows were examined for signs of clinical mastitis by the herd personnel immediately before milking. Clinical mastitis was characterized by the presence of abnormal milk or by signs of inflammation in one or more quarters. Digestive problems were characterized by diarrhea, bloat, or displacement of abomasum. Respiratory problems were characterized by increased respiratory frequency associated with fever and presence of increased lung sounds at auscultation.

Estrous cyclicity before synchronization of the estrous cycle was determined either by progesterone con-

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