Long-term Consequences of Clinical Diseases Postpartum on Lactation and Reproductive Performances in Dairy Cows

Eduardo de Souza Ribeiro, Murilo Romulo Carvalho, José Felipe Sprícigo, and Bruna Mion
Department of Animal Biosciences, University of Guelph, Guelph, ON, Canada
Email: eribeiro@uoguelph.ca; Phone: +1 (519) 824-4120 Ext. 56516

Introduction

Clinical diseases caused by microbial infection and tissue injury are prevalent in postpartum dairy cows (Santos et al., 2010; Ribeiro et al., 2013; 2016a). Approximately one-third of dairy cows have at least one clinical disease in the first 3-weeks of lactation, and they represent 60 to 80% all clinical cases occurring in lactating cows. The most common clinical diseases observed in dairy herds are metritis, mastitis, digestive problems, lameness, and respiratory problems. The incidence of these diseases in the first 2-months of lactation of 8,268 cows in eight large dairy herds in USA was 21.3, 13.8, 6.4, 5.5, and 2.4%, respectively (Ribeiro and Carvalho, 2017). Combined, these diseases affected 40% of all cows.

The increased susceptibility to diseases in the early postpartum is mostly explained by reduced immunocompetence of dairy cows during this period. The nutritional status and associated metabolic scenario observed postpartum impair function of immune cells and increase the susceptibility to opportunistic microbial infections (Sordillo, 2016). In addition, the enlarged uterus postpartum contains placenta remnants and lochia that favor proliferation of microbes and development of uterine infections (Sheldon et al., 2009).

Cows diagnosed with clinical diseases postpartum are normally treated with drugs or support therapy and, in most cases, health and metabolism seem to be normal by the end of the first month postpartum. However, cows with clinical disease postpartum have reduced lactation and reproductive performances compared with cows that are healthier postpartum or more resilient to the transition challenges. This review summarizes our current understanding of the long-term effects of clinical diseases postpartum on performance of dairy cows and the associated biological mechanisms mediating such effects.

Clinical Disease Postpartum Impairs Fertility

Cows with clinical diseases have delayed resumption of estrous cyclicity postpartum (Santos et al., 2010; Ribeiro et al., 2013), which prolongs the interval between calving and first artificial insemination (AI) postpartum. In general, delayed first breeding causes reproductive inefficiency and economic losses (Ribeiro et al., 2012). Timed AI programs can be used to assure proper time of first AI postpartum. However, the odds of being diagnosed pregnant 45 days after a timed AI is 30% smaller for cows with postpartum disease compared with cows that did not have postpartum disease (Ribeiro and Carvalho, 2017). Further, the odds of pregnancy losses after day 45 of gestation are 2-times greater, and the odds of calving from first breeding postpartum are 42% smaller for cows with postpartum diseases compared with cows that did not have disease (Ribeiro and Carvalho, 2017). Therefore, the impact of diseases is significant even when cows are subjected to timed AI programs. No differences in ovulation after synchronization of the estrous cycle or expression of estrus at timed AI were observed between cows that had or did not have

postpartum diseases (Ribeiro and Carvalho, 2017). Therefore, the observed difference in pregnancy per breeding would be a result of reduced fertilization of oocytes and/or greater embryonic losses occurring before pregnancy diagnosis.

To evaluate the impact of diseases on fertilization of oocytes, early embryo development and survival to morula stage, health information of 597 lactating cows was collected from parturition until first AI postpartum, and uterine flushing for recovery of ova-embryos was performed 5 or 6 days after AI. A total of 419 ova-embryos were recovered and evaluated for stage of development and quality. Cows with diseases before AI had reduced proportion of cleaved, live, and high-quality embryos relative to ova-embryos recovered (Ribeiro et al., 2016a). Within cows with a recovered cleaved embryo, the odds of recovering a live embryo were reduced by 53.6% in cows with disease. The reduction in cleaved embryos is likely caused by reduced fertilization of oocytes. Thus, the results indicate that postpartum disease reduces fertilization of oocytes and survival of zygotes in the first week of development.

To evaluate the impact of diseases on preimplantation conceptus elongation, health information of 148 lactating cows was collected from parturition until first AI postpartum, and uterine flushing for recovery of conceptuses was performed 15 or 16 days after AI. Cows with diseases had shorter conceptuses and reduced concentration of interferon (IFN)-τ in the uterine flush (Ribeiro et al., 2016a). These results were supported by a second experiment that evaluated the transcript expression of IFN stimulated genes (ISGs) in peripheral blood leukocytes (PBL) on day 19 after AI (Ribeiro et al., 2016a). Interferon-τ produced by the elongating conceptus in utero reaches maternal circulation and induces changes in gene expression in peripheral tissues including PBL (Oliveira et al., 2008). Within cows that did not have disease before breeding, the expression of two ISGs (ISG15 and RTP4) was increased in cows later diagnosed as pregnant compared with those diagnosed not pregnant. However, this difference in gene expression of ISGs according pregnancy status was not significant in cows with diseases before AI, suggesting that production of IFN-τ by the elongating conceptuses in utero of cows that had postpartum diseases was reduced (Ribeiro et al., 2016a).

Uterine Disease and Non-Uterine Disease Cause Similar Impact on Fertility

In order to characterize the impact of diseases on reproductive biology of cattle, it is also important to understand how the impact is mediated, so that strategies to mitigate this negative association between diseases and reproduction might be developed. The site of infection or tissue injury is an important factor because the impact on reproduction and the mediator mechanism might change accordingly. Uterine diseases cause endometrial lesions that have detrimental effects on tissue integrity and physiology, hence suboptimal embryonic development and survival. Diseases that occur outside the uterus (i.e. mastitis, lameness, acidosis) might have effects on reproductive biology that are mediated by a physiological response to infection or injury to tissues.

Ribeiro et al. (2016a) compared the effects of the uterine diseases (metritis) and non-uterine diseases (mastitis, lameness, digestive and respiratory problems) on reproduction of lactating dairy cows. Uterine and non-uterine diseases had similar impact on reproduction of dairy cows.

Both type of disorder decreased pregnancy per breeding on day 45 after breeding, increased pregnancy loss after day 45 of gestation, and decreased calving per breeding. Moreover, the two types of diseases have additive negative effects on reproductive outcomes. Cows that had both uterine and non-uterine diseases were 41% less likely to be pregnant on day 45 after breeding (adjusted odds ratio [AOR] = 0.59; CI = [0.47-0.75]), 3-times more likely to lose pregnancy after day 45 of gestation (AOR = 3.06; CI = [1.67-5.60]), and 60% less likely to calved from first breeding postpartum (AOR = 0.40; CI = [0.28-0.58]) compared with cows that did not have disease before breeding. The effects of diseases on the development to morula and conceptus elongation were also similar between uterine and non-uterine diseases (Ribeiro et al., 2016a).

Clinical Diseases Impairs Both Oocyte Quality and Uterine Environment

The interval from the activation of primordial follicles to the formation of preovulatory follicle is estimated to last 180 days (Fair, 2003), in which the majority of time would be spent in the pre-antral stages (138 days), and less time in the antral stages (42 days; Lussier et al., 1987). During folliculogenesis, disease could potentially disturb the follicular environment and oocyte developmental competence without apparent effects on growth and ovulation (Bromfield et al., 2015). Thus, a potential impact of postpartum disease on preantral or antral follicles is a plausible mechanism mediating the long-lasting effects of disease on reproduction.

If reduced oocyte developmental competence was the sole explanation for the long-lasting effects of postpartum diseases on reproduction, then fertility of cows in an embryo transfer (ET) program would not be affected by the occurrence of postpartum diseases. On the other hand, if diseases had an impact on fertility of cows receiving a viable embryo on day 7 of the cycle, then uterine environment should mediate at least part of the effects of disease on fertility of cattle. To test these hypotheses, information on the incidence of postpartum diseases, pregnancy and calving per breeding, and late pregnancy losses were collected in a large dairy farm using both AI and ET as part of the reproductive management for lactating cows (Ribeiro et al., 2016a). Disease affected all reproductive outcomes, and the interaction with breeding technique was not significant. Similar results were obtained when only uterine disease or only non-uterine diseases were considered, thereby suggesting that both types of disease have long-lasting effects on the uterine environment that impairs the ability to support pregnancy to term (Ribeiro et al., 2016a).

Furthermore, ET increased the proportion of cows calving from first breeding compared with AI. The difference, however, was significant only in cows that had disease before breeding. The improvement in calving per breeding observed in cows that had disease when receiving ET suggests that oocyte quality and/or oviduct environment is also affected by disease. Supporting evidence for this interpretation is the slightly smaller change in adjusted odds ratios attributable to disease in cows receiving ET compared with those receiving AI (Ribeiro et al., 2016a). Thus, reduced oocyte competence is a likely component in the carryover effects of disease in fertility of cows receiving AI, and impaired uterine environment is a reason for carryover effects of diseases in fertility of cows receiving AI and cows receiving ET.

Conceptus cells sense changes in uterine environment and respond accordingly. Therefore, studying the transcriptome of conceptus cells could contribute to the discovery of a mechanism

mediating long-lasting effect of inflammatory diseases on uterine biology. Ribeiro et al. (2016a) compared the transcriptome of conceptuses on day 16 of development from cows that had or did not have non-uterine diseases before AI. Five conceptuses recovered from cows that had non-uterine diseases before breeding were matched with five conceptuses of cows that did not have disease before breeding and used for transcriptome analyses. Only a small number (n = 35) of transcripts were differently expressed between the two groups. Nonetheless, functional analysis of these transcripts revealed that changes in the transcriptome of conceptus cells recovered from cows with diseases before breeding resemble an inflammatory response. Three proinflammatory molecules, lipopolysaccharide, IFN-γ and tumor necrosis factor were predicted to be potential upstream regulators of the changes in transcriptome observed in conceptuses recovered from disease cows. Moreover, the potential downstream consequences of these changes would include cell activation, particularly immune cells, and possibly problems with tissue rejection by immune system. These effects could result in rejection of the conceptus tissue by the maternal immune system and pregnancy loss.

Impact of Disease Postpartum on Fertility Goes Beyond First Breeding

All data discussed up to this point refer to fertility outcomes of the first breeding postpartum, when cows are between 50 to 90 days in milk. Although it is clear that fertility in the first breeding is affected by diseases in the early postpartum, this data does not examine how long the effects of disease postpartum last. Would be possible to delay the first breeding to avoid the negative effects of disease postpartum or a bad transition period? Are later breeding also affected?

Carvalho et al. (2018) investigated the impact of clinical diseases that occurred in the first 21 days postpartum (ClinD21) on reproductive performance up to 305 days in milk. In addition, to detailed health information, records of all breeding performed from the end of voluntary waiting period up to 305 days in milk were examined. Although the interval from calving to first breeding was not different between cows that had or did not have ClinD21, pregnancy rate up to 305 DIM was reduced in cows that had ClinD21 (adjusted hazard ratio [AHR] = 0.81), which resulted in extended interval from calving to pregnancy (NoClinD21 = 133.5 vs. ClinD21 = 147.1 d) and reduced proportion of cows diagnosed pregnant within 305 DIM (NoClinD21 = 88.4 vs. ClinD21 = 81.4%). When individual breeding were analyzed, cows that had ClinD21 presented reduced pregnancy per AI for breeding performed before 150 DIM, reduced calving per AI for breeding performed before 200 DIM, and greater pregnancy losses for all breeding up to 305 DIM. Therefore, diseases in the early postpartum have consequences for reproduction of lactating cows up to 10 months after clinical resolution of the disease, and delaying first breeding postpartum is not expect to minimize the impact of disease on reproduction.

More than Fertility - Lactation Performance Is Also Impaired

In addition to reproduction, Carvalho et al. (2018) also investigated the impact of ClinD21 on milk production up to 305 days in milk. Cows that had ClinD21 produced, on average, 410 kg less milk, 17 kg less fat, and 12 kg less protein compared with cows that did not have ClinD21. The reduction in lactation performance was also associated with frequency of ClinD21. For instance, 305-d yield of milk was 357 and 703 kg lesser in cows with a single and multiple ClinD21, respectively, when compared with cows that did not have ClinD21. In addition, cows that had ClinD21 had a lower

and delayed peak in production when compared with cows that did not have ClinD21. Similar to reproduction, uterine and non-uterine diseases such as mastitis had similar impact on milk production up to 305 days in milk, and both type of disease had additive negative effects on production. The observed differences in production could not be explained by differences in production observed during the clinical presentation, suggesting that disease in the early postpartum have long-term consequences on production traits.

In a second study performed by Carvalho et al. (2018), data regarding health postpartum and 305-d yields of milk, fat and protein were collected from 2,415 primiparous cows that had genomic information from a low density panel of single nucleotide polymorphisms. Genomic estimated breeding values (EBV) values for milk, fat, and protein were used to predict 305-d yields of milk, fat, and protein. Genomic EBV values and predicted 305-d yields of milk, fat, and protein were similar between cows that had ClinD21 and those that did not have ClinD21. However, the observed 305-d yields of milk, fat, and protein were reduced by 345, 10 and 10 kg, respectively, in cows that had ClinD21 compared with cows that did not have ClinD21. Moreover, the absolute differences between predicted and observed 305-d yields were larger in cows that had ClinD21 compared with cows that did not have ClinD21. These results suggest that 1) observed differences in production between cows that had or did not have ClinD21 are not related to distinct genetic potential to produce milk, and 2) diseases in the early postpartum compromises the accuracy of genomic predictions of production traits.

Implications for Nutritional Management

Prevention of postpartum inflammatory diseases is unquestionably the best approach to reduce the impact of diseases on fertility of cattle, and strategies to minimize the incidence of postpartum diseases are mostly associated with nutritional management pre- and postpartum (LeBlanc et al., 2006; Santos and Ribeiro, 2014).Nonetheless, understanding the mechanism mediating the impact of disease on reproductive biology of cattle could lead to new strategies for mitigation of the negative consequences of diseases. Assuming that inflammation caused by clinical diseases is the major mediator of subfertility in cows with postpartum diseases, control of inflammation during the clinical presentation of the disease could potentially mitigate the effects of inflammation on reproduction. McDougall et al. (2016) performed a randomized clinical trial testing the hypothesis that addition of a nonsteroidal anti-inflammatory drug (meloxicam) to antimicrobial treatment of clinical mastitis would improve subsequent fertility of dairy cows. Cows treated with meloxicam had greater conception risk in their first insemination postpartum and greater proportion of cows pregnant by day 120 after calving compared with the control group. The results indicate that controlling inflammation during clinical presentation of an inflammatory disease might improve subsequent reproductive performance in dairy cows. A nutraceutical alternative for control of inflammation is reducing ratio of omega-6 to omega-3 fatty acids in the diet of postpartum cows (Greco et al., 2015), which could also minimize the effects of inflammatory diseases on reproduction. Moreover, growing understanding of the differences in reproductive biology of cows that had or did not had diseases postpartum might lead to the development of diets that supply specific shortages of nutrients or stimulating factors that promote oocyte developmental competence and uterine receptivity to pregnancy, consequently improving fertility of dairy cows.

Conclusions

Clinical diseases occurring before breeding are very prevalent in dairy cows and have long-lasting effects on subsequent fertility, milk production, and survival in the herd. Diseases caused by infection in the reproductive tract and diseases caused by infection outside the reproductive tract seem to have similar consequences for reproduction and lactation performance of dairy cows and, when combined, have additive negative effects. The consequences of diseases on fertility does not seem to be mediated by a single mechanism, rather a combination of multiple mechanisms that have additive negative effects, which include reduced BCS at the time of breeding, reduced developmental competence of oocytes, and altered uterine environment. Even though cows with clinical health problems early postpartum are treated and clinical resolution is generally obtained within few days of treatment, pregnancy per AI up to 150 days in milk, fetal survival of pregnancies established up to 305 days in milk, milk production and survival up to 305 days in milk are all impaired in this subgroup of cows. In addition to prevention of diseases, early diagnosis, fast intervention with adequate treatment, and control of inflammation during clinical presentation of the disease mitigate the impact of health problems on reproductive biology of cattle. It is increasingly evident that animal health, not only at the time of breeding or pregnancy development but also in the period preceding breeding, is imperative for optimal reproduction of lactating cows and should always be considered in herd evaluations and management decisions.

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