J. Dairy Sci. 101:1–12
https://doi.org/10.3168/jds.2017-13469

Lipids as regulators of conceptus development: Implications for metabolic regulation of reproduction in dairy cattle[1]

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ABSTRACT

Pregnancy losses are substantial in dairy cattle and threaten reproductive efficiency. A substantial proportion of these losses occur during early stages of conceptus development, including the elongation phase. Elongation of the preimplantation conceptus is a prerequisite for maternal recognition, implantation, and survival of pregnancy. The onset of elongation occurs when concentrations of lipids in endometrial epithelial cells are increased, and it requires substantial coordination of lipid metabolism by conceptus cells. The nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) seems to have a central role in coordinating gene expression in trophectoderm cells at the onset of elongation, particularly of genes involved in lipid metabolism. Numerous fatty acids are natural ligands of PPARγ and their concentrations in the histotroph are likely important to PPARγ activity and its downstream effects on conceptus biology. Changes in concentration or composition of fatty acids in the histotroph could alter conceptus development. Inflammatory diseases and excessive loss of body reserves are prevalent problems in postpartum dairy cows and represent important risk factors for early pregnancy loss in the subsequent breeding period. Although cows affected by these conditions likely have reduced developmental capacity of oocytes, embryo transfer studies indicate that impaired uterine environment also contributes to their subfertility. Long-lasting effects of these conditions on energy and lipid homeostasis might alter composition of the histotroph and could help explain developmental failures occurring during conceptus formation attributable to impaired uterine environment. Targeting of uterine lipid metabolism and PPARγ activity during preimplantation conceptus development through prevention of disease and optimized feed intake postpartum and through nutraceutical diets at the time of breeding are potential strategies to improve pregnancy survival and consequently reproductive efficiency in dairy cows.
Key words: conceptus, lipids, inflammation, metabolism, pregnancy

INTRODUCTION

Reproduction is a major component in dairy sustainability because it affects the overall milk yield in a herd and its production efficiency (Ribeiro et al., 2012). Evaluation of reproductive data from DHI herds in North America indicates that overall reproductive efficiency, although still suboptimal, has improved in recent years. For instance, the average calving interval of US Holstein cows decreased from 423 d in 2005 to 403 d in 2013 (Norman et al., 2016). In Canada, average 21-d pregnancy rate of herds in Ontario and western Canada increased from 12.5% in 2005 to 15.0% in 2013 (Figure 1). Interestingly, the observed improvements are explained by better submission of cows to AI and occurred without any significant change in the average pregnancy per AI (**P/AI**). For example, the interval from calving to first breeding of US Holstein cows was reduced from 87 d in 2005 to 78 d in 2013 but P/AI stayed consistently close to 30% during the same period (Norman et al., 2016). The submission rate in Canadian herds increased from 33.8% in 2005 to 41.5% in 2013, but the average P/AI was close to 38% during the same period (Figure 1). Thus, low P/AI remains a major contributor to suboptimal reproduction in lactating dairy cows and precludes faster advances in pregnancy rate.

The main contributor to low P/AI in lactating dairy cows is early pregnancy loss. Ribeiro and coauthors (2016a) performed 597 flushings in lactating Holstein cows on d 5 or 6 after synchronized ovulation for first AI postpartum and, from all structures recovered (n = 419), 83% were fertilized and 67% were considered to be viable embryos (Figure 2). The difference between fertilized oocytes and live embryos indicates that 19% of the zygotes were lost in the first week of development. The average P/AI on d 30 after first timed AI postpartum

Received July 10, 2017.
Accepted September 30, 2017.
[1]Presented as part of the Physiology and Endocrinology Symposium: Mediators of Effects of Stress on Reproduction, Growth, and Lactation at the ADSA Annual Meeting, Pittsburgh, Pennsylvania, June 2017.
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in the same herds was 41% for cows with synchronized ovulation at the end of the timed AI program. Thus, it was estimated that 39% of the live morulas would fail to survive until the end of the fourth week of development and, therefore, represent an important impairment of reproductive performance. During this period of development, intricate events in developmental biology require extensive coordination between the developing conceptus and the endometrium. Among these events, elongation of the preimplantation conceptus has central importance because it is a requirement for maternal recognition of pregnancy, implantation, and onset of placentation, such that failure of elongation is likely an important cause of pregnancy losses in cattle.

Recent research has identified lipid metabolism in utero as a major component in successful elongation of the preimplantation conceptus and consequent survival of pregnancy in dairy cows (Ribeiro et al., 2016b,c). In addition, lipid metabolism in lactating dairy cows is highly dynamic because of fluctuations in energy requirements, intake, and partitioning (Drackley, 1999), which has potential implications for lipid homeostasis of the uterus and for the biology of conceptus development. This review summarizes recent work describing the importance of uterine lipid metabolism in conceptus development; the dynamics of lipid metabolism in the dairy cow influenced by lactation, health, and dietary management; and the implications for uterine biology and reproductive success in lactating dairy cows.

LIPID METABOLISM OF TROPHECTODERM CELLS AS MODULATORS OF CONCEPTUS ELONGATION

After hatching from the zona pellucida around d 9 of development, the spherical bovine embryo remains free-floating in the uterine lumen. Cell proliferation of the embryoblast and trophoblast leads to formation of an ovoid conceptus by d 13. Up to this point, endometrial physiology is coordinated mainly by progesterone (Lonergan et al., 2016; Spencer et al., 2016a) and there is no major distinction between the endometrium of a pregnant and a nonpregnant cow (Forde et al., 2011; Bauersachs et al., 2012). Around d 14, the 1-mm ovoid conceptus starts to elongate by rapid proliferation and reorganization of trophectoderm cells, and becomes a filamentous structure of approximately 200 mm by d

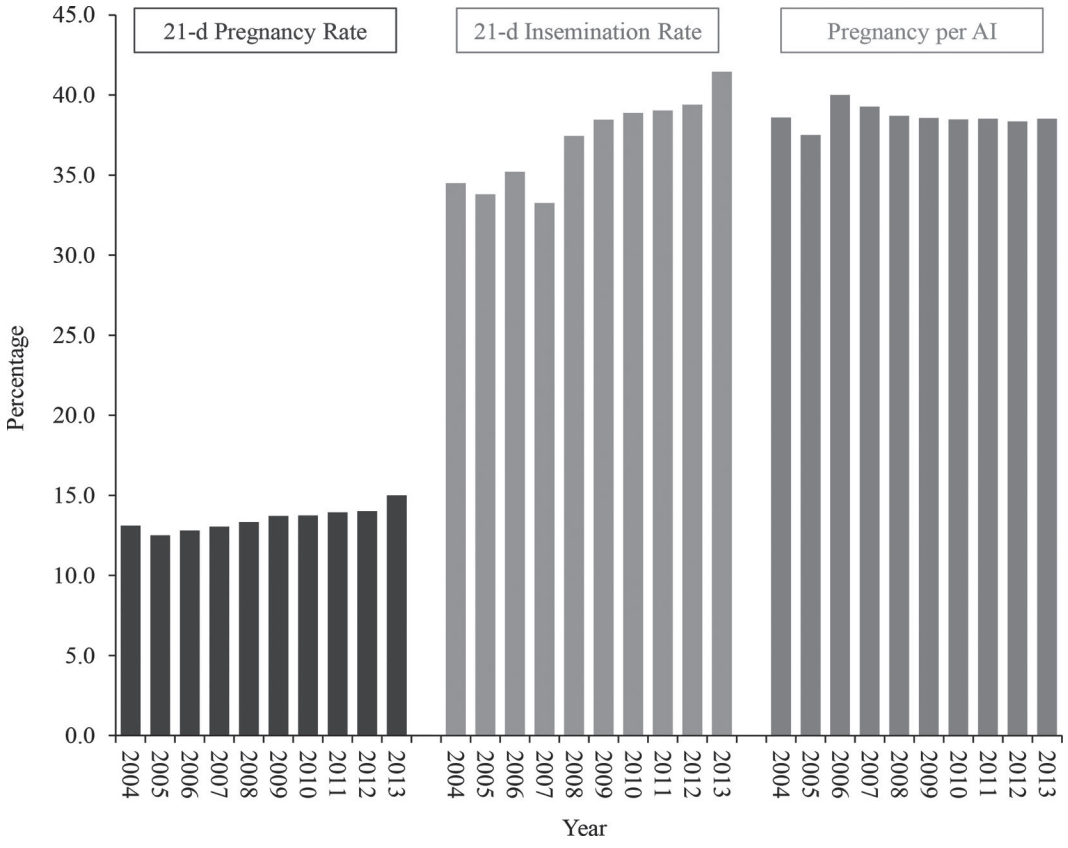

Figure 1. Recent reproductive indices of Ontario and western Canadian DHI herds. Each herd enrolled in the program contributed with a single annual average number. Data provided by CanWest DHI (Guelph, ON, Canada). Color version available online.