Nutrient Prioritization in Dairy Cows Early Postpartum: Mismatch Between Metabolism and Fertility?

JLMR Leroy1, T Vanholder1, ATM Van Knevel2, I Garcia-Ispierio3 and PEJ Bols1

1Veterinary Centre Someren, Someren; 2Adaptation Physiology Group and Animal Nutrition Group, Wageningen Institute of Animal Sciences, Wageningen University, Wageningen, The Netherlands; 3Department of Animal Health and Anatomy, Autonomous University of Barcelona, Barcelona, Spain

Contents

For several decades, researchers worldwide report a decrease in fertility in high-yielding dairy cows, most probably based on conflicting metabolic and reproductive needs. The dairy herd manager’s success at improving milk production has been accompanied by a negative trend for the most visible reproductive parameters such as calving intervals, number of days open and number of inseminations needed per pregnancy. In parallel, many research groups studied the metabolic and endocrine factors that influence follicular growth and the developmental competence of oocytes and embryos. In the past, herd managers and reproductive biologists each tried to tackle the same problems with limited consultation. More recently, the situation has improved significantly and theriogenologists, nutritionists and veterinarians now conduct research in multidisciplinary teams. This review paper starts in a general way by discussing nutrient prioritization towards the udder to guarantee milk production and by describing interactions between the somatotropic and gonadotropic axis.

Introduction

Disappointing reproductive performance in high-producing dairy herds is a global problem, characterized as multifactorial and urged a multidisciplinary approach in which animal scientists, veterinarians and molecular biologists were required to unravel the complex pathogenesis of this ‘subfertility syndrome’. After all, producing a calf at regular intervals is considered a prerequisite for profitable lactational performance (Royal et al. 2000; Huirne et al. 2002). After giving birth, the process of becoming pregnant again in dairy cows starts with clearance and involution of the uterus followed by resumption of ovarian activity. This should result in the completion of the growth of a healthy follicle, enclosing a competent oocyte, and ultimately in oestrus, ovulation, fertilization and uterine attachment by a viable embryo. Any upset of these balanced and fine-tuned biological and mechanical events leads to failing reproduction – and this is exactly where the shoe pinches in our modern dairy herds.

The subfertility syndrome can be divided into two major sub-problems. First of all, up to 50% of modern dairy cows display abnormal oestrus cycles postpartum leading to prolonged calving to first insemination intervals (Opsomer et al. 1998). In this context, especially instability within the hypothalamo–pituitary–ovarian–uterine axis has been studied thoroughly (Lucy 2001; Butler 2003). The concomitant reduced oestrus expression or even anoestrus, cyst formation and delayed first ovulation have been extensively documented (Beam and Butler 1997; de Vries and Veerkamp 2000; Lopez et al. 2004; Vanholder et al. 2006a).

Secondly, attention was focussed on disappointing conception rates (Bousquet et al. 2004) and the increasingly high incidence of early embryonic mortality (Dunne et al. 1999; Mann and Lamming 2001; Bilo-deau-Goeseels and Kastelic 2003). Fertilization of oocytes from high-genetic merit cows resulted in significantly lower blastocyst yields in vitro, irrespective of milk production as such (Snijders et al. 2000). Embryo quality was also reduced in high-producing dairy cows compared with non-lactating counterparts (Wiltbank et al. 2001; Leroy et al. 2005a). A high proportion of non-viable embryos were found in lactating cows compared with non-lactating cows (Sartori et al. 2002). Approximately 70–80% of the total embryonic and foetal losses typically occur during the early embryonic, pre-attachment period (Santos et al. 2004a) (for review, see Leroy et al. 2007).

Modern dairy cows, albeit sub-fertile, produce vast amounts of milk mainly because of significant genetic improvements, combined with nutritional management optimized towards lactation. Based on almost unchanged heifer fertility, we can conclude that the reproductive processes of modern dairy cattle are essentially normal when lactation demands are not imposed (Lucy 2007). Why do modern dairy cows prioritize milk production at the expense of sustained reproductive efficiency? In this review, we aim to answer this question. Are high milk yields and good fertility outcomes conflicting interests metabolically speaking?

From Phylogenetically Driven to Genetically Enforced Nutrient Prioritization: The Consequences on Metabolism

From a biological point of view, it makes sense for mammals in early lactation to favour milk production over fertility: this we can refer to as nutrient prioritization (Lucy 2003). As nutrition becomes scarce, the lactating dam will preferentially invest the limited resources in the survival of living offspring rather than gambling on the oocyte that is yet to be ovulated.
fertilized and cared for during an entire gestation. This maternal catabolic mechanism, also genetically programmed, should maximize the chance of survival of the newborn offspring (Silvia 2003). Over the past 40 years, the focus of dairy industry has been on maximizing milk yield, thereby creating a 'nutrient highway' from the daily ration and body reserves (estimated on 74% body fat and 6% body protein; Tamminga et al. 1997) directly to the udder to sustain milk production.

Nutrient requirements of the gravid uterus late in gestation impose a catabolic status on the dairy cow. Following parturition, an additional demand for glucose, fatty acids and protein is established as milk production starts. During this transition period, cows are unable to compensate for such increased energy demands by increasing feed intake, and this results in negative energy balance (NEB). Drastically reduced insulin concentrations bring approximate energy mobilization and partitioning of energy to the udder. Hypoinsulinæmia promotes gluconeogenesis in the liver (up to 4 kg glucose each day) and acts as a massive lipolytic trigger. The mobilized non-esterified fatty acids (NEFAs) serve as an alternative energy source for other tissues to preserve glucose, which is preferentially used by the mammary gland to form lactose (Vernon 2002). NEFAs are predominantly transported to the liver where they are oxidized to provide energy or transformed into ketone bodies, again an alternative energy source elsewhere in the body. An aberrant over-load of the liver by NEFAs can induce steatosis and disturbed liver function (Herdt 2000). Hormone-sensitive lipases in adipose tissue of high-yielding dairy cows have an increased sensitivity to lipolytic stimuli (such as low insulin, and high catecholamines or glucocorticoids concentrations). In other words, high-yielding dairy cows have been genetically selected to partition even more energy reserves into milk production (Coffey et al. 2004). A higher dietary energy intake will therefore result in greater milk production, but a similar energy imbalance remains, with no beneficial effects on body condition score (BCS) at all (Patton et al. 2006).

A series of biological mechanisms bring an approximate prioritization for milk production at the cost of body reserves in early postpartum dairy cows. First of all, the udder benefits because it does not need insulin to facilitate glucose uptake into cells by the glucose-transport molecules, GLUT 1 and 3, while most other tissues predominantly express insulin-dependent GLUT 4 (Zhao et al. 1996). Secondly, using repeatedly intravenous glucose-tolerance tests, we recently found a temporary suppression of pancreatic function in early postpartum high-yielding dairy cows and this was correlated with elevated NEFA concentrations (Bossaert et al. 2007). In vitro, high NEFA levels have toxic effects on pancreatic cells (Cnoo et al. 2001; Maedler et al. 2001). Thirdly, in the early postpartum period, low insulin concentrations uncouple the growth hormone (GH)–insulin like growth factor 1 (IGF-I) axis in the liver because of down-regulation of GH 1A receptors and this can be restored by increasing insulin (Butler et al. 2003). As IGF-I production in the liver is suppressed, the negative feedback of IGF-I is removed at the level of the hypothalamus/pituitary, and GH concentrations increase. High GH concentrations not only stimulate milk production but also provoke liver gluconeogenesis and lipolysis in adipocytes. The resulting high blood NEFA and GH concentrations antagonize insulin action and create a further state of peripheral insulin resistance (Lucy 2007; Pires et al. 2007). In this way even more glucose is conserved to be available for lactose synthesis.

Fatter cows tend to mobilize more body fat because of reduced appetite (Garnsworthy and Topps 1982). It is broadly accepted that genetic selection for milk production results in greater BCS loss, further suggesting that energy is partitioned towards the udder (Roche et al. 2006). An excessive BCS loss during the transition period is a major risk factor for health and fertility disorders (Roche et al. 2007), which stresses the importance of BCS monitoring early postpartum as a management tool (Chagas et al. 2007).

**Interactions Between the Somatotropic and the Gonadotropic Axis**

Extensive scientific research has shown that mechanisms that regulate energy and nutrient distribution in the somatotropic system may affect the reproductive system at different levels of the hypothalamo-pituitary-ovarian axis (Roche 2006; Chagas et al. 2007). Within the hypothalamus, interactions between the gonadotropic and somatotropic systems may occur in the pre-optic area (Blache et al. 2006, 2007). This region produces the releasing hormones that control the secretion of both gonadotropins and somatotropin (Kacsoh 2000). In addition, it plays a crucial role in integrating appetite (Wynne et al. 2005), oestrus behaviour (Pfaff 2005) and sensing of the nutritional status (Wade and Jones 2004). Consequently, metabolic inputs in the hypothalamus may have divergent effects on the gonadotropic and somatotropic axis, i.e. stimulation of GH production may be accompanied by inhibition of GnRH secretion (Zieba et al. 2005). The hormones/metabolites that are most likely to exert a signalling function are glucose and insulin. Low postpartum insulin and glucose concentrations suppress hypothalamic GnRH secretion and subsequent pituitary LH release (Diskin et al. 2003; Ohkura et al. 2004). By activation of specific neurons in the forebrain, peptides such as neuropeptide Y and catecholamines are released, which suppress the hypothalamic GnRH pulse generator (Ichimaru et al. 2001; Diskin et al. 2003; Wade and Jones 2004). Other metabolic signals may involve leptin and NEFA, although their role currently remains unclear (Liefers et al. 2003; Wade and Jones 2004; Amstalden et al. 2005).

At ovarian level, follicular growth and development seems to be directly influenced by altered insulin, IGF-I, leptin and NEFA levels. Because insulin locally stimulates follicular growth, maturation and steroidogenesis, reduced postpartum concentrations are linked to ovarian dysfunction (Gutiérrez-Aguilar 1997; Landau et al. 2000; Armstrong et al. 2002a; Butler et al. 2004; Vahholder et al. 2005a; Kawashima et al. 2007). Long-term treatment with exogenous bovine somatotropin clearly increased the number of small follicles (Bols et al. 1998).
Gong (2002) showed that the beneficial effects of insulin on ovarian functions are independent of changes in GnRH/LH release. In ovarian cells, insulin-independent GLUT-1 and GLUT-3 are the major glucose transporters, while the insulin-dependent GLUT-4 only plays a supportive role (Nishimoto et al. 2006). Hence, insulin may exert its effects through mechanisms other than mediating glucose uptake.

Together with insulin, the IGF system plays an important role in follicle growth and development by acting directly on ovarian cells (Spicer and Echternkamp 1995; Gutiérrez-Aguilar 1997; Beam and Butler 1999; Webb et al. 1999; Gong 2002). Consequently, low circulating IGF-1 concentrations negatively influence the onset of postpartum ovarian activity and seem involved in the development of cystic ovarian follicles (Beam and Butler 1997; Kawashima et al. 2007; Ortega et al. 2007). The effects of leptin on steroidogenesis and cell proliferation are, yet, dependent on the circulating concentrations of IGF-1, LH and insulin (Spicer and Francisco 1997, 1998; Spicer et al. 2000).

At ovarian level, NEFAs may affect follicular growth and development by acting directly on follicle cells. Adding NEFAs in vitro, at concentrations measured in follicular fluid (FF) during NEB has detrimental effects on follicle cell viability and function (Leroy et al. 2005b; Vanholder et al. 2005b, 2006b).

In conclusion, metabolic changes induced by the somatotropic system to sustain a high milk yield also affect the reproductive system. By acting at different levels of the hypothalamo-pituitary-ovarian axis, altered hormone and metabolite levels exert a negative effect on follicle growth, development and probably ovulation.

Consequences for Oocyte Quality

Researchers assume the existence of a carry-over effect of the adverse metabolic conditions during primary follicle growth early postpartum on the health of the pre-ovulatory follicle 2–3 months later (Britt 1992). Such follicles may be less capable of producing adequate amounts of oestrogens and progesterone (following ovulation) and might be doomed to contain an oocyte of inferior quality (Britt 1992; Roth et al. 2001a). The developmental capacity of the oocyte is intrinsically linked to the growth phase and health of the developing follicle (Bilodeau-Goeseels and Panich 2002; Sutton et al. 2003; Lequarre et al. 2005). Last but not least, diet composition can also alter the endocrine and metabolic micro-environment of the developing oocyte (Boland et al. 2001; McEvoy et al. 2001; Kenny et al. 2002).

A deviant endocrine environment, because of or as a consequence of a NEB can alter oocyte quality through various mechanisms such as spindle formation, prolonged follicular growth and resumption of meiotic progression, all of which has been extensively reviewed earlier (Leroy et al. 2007). Only a few studies have examined possible effects of NEB-associated low glucose, elevated β-hydroxybutyrate (β-OHB) or NEFA concentrations on oocyte quality. Apart from indirect effects of hypoglycaemia in early postpartum dairy cows (through an effect on LH secretion or ovarian responsiveness to gonadotrophins), hypoglycaemic conditions (e.g. clinical ketosis) are reflected in the microenvironment of the pre-ovulatory oocyte, and can compromise the oocyte’s developmental capacity, because glucose is an indispensable molecule for proper oocyte maturation (Bilodeau-Goeseels 2006; for review see Sutton et al. 2003; Leroy et al. 2004, 2006). Kruij and Kemp (1999) suggested possible direct toxic effects of high NEFA concentrations at the ovarian level of the ovary. Indeed, in an in vitro maturation model, saturated long-chain fatty acids, reduced rates of maturation, fertilization, cleavage and blastocyst formation. Apoptosis, and even cumulus cell necrosis, during maturation could explain these observations (Leroy et al. 2005b). Finally, elevated ammonia and urea concentrations in the FF, because of an unbalanced diet and protein catabolism were toxic for the oocyte (Sinclair et al. 2000; De Wit et al. 2001; Leroy et al. 2004).

Early Pregnancy in High-producing Dairy Cows: Embryo Quality

Early embryonic death is a major cause of reproductive failure in dairy cows accounting for up to a total 80% pregnancy losses (Santos et al. 2004a). There are four major factors impinging on embryo quality in the specific case of high-producing dairy cows: gamete quality, corpus luteum quality combined with the circulating progesterone concentration, uterine involution and nutrition. Yet, only those that are related to NEB will be discussed.

Adverse pre-ovulatory conditions, such as NEB, may have carry-over effects on embryo metabolism and viability resulting in early embryonic mortality (Yaakub et al. 1999; Lozano et al. 2003; Rhoads et al. 2006). Distinguishing oocyte effects on embryo quality from post-fertilization influences is extremely difficult. Only at least a 6-day-old embryo can be transferred to a recipient to assess the impact of uterine environment on embryo quality. Lucy (2007) supports the concept that fertility could be improved in dairy cows by using embryo transfer and thus circumventing the period of oocyte and early embryonic development.

Well-timed and balanced post-mating progesterone concentrations are vital for zygote viability as progesterone modulates the endometrial secretions, and thus optimal uterine receptivity (McEvoy et al. 1995). It has been suggested that disappointing pregnancy results in modern dairying are partially caused by the retarded onset of the progesterone rise and suboptimal progesterone concentrations during the luteal phase (Mann and Lamming 2001). Furthermore, the typical NEB observed early postpartum can reduce the number of ovulatory oestrous cycles preceding AI which may hamper adequate uterus preparation (Butler 2003). Villa-Godoy et al. (1988) showed that cows in NEB postpartum had lower progesterone concentrations during the first three ovarian cycles following calving. Despite larger volumes of luteal tissue, compared with non-lactating heifers, maximal progesterone concentrations in lactating cows are lower, possibly because of a higher rate of degradation in the liver (Sangsritavong et al. 2002; Sartori et al. 2004; Wiltbank et al. 2006).

© 2008 The Authors. Journal compilation © 2008 Blackwell Verlag
Good postpartum uterine involution, comprising endometrium repair and evacuation of bacterially contaminated contents, is of critical importance for reproductive performance (for review, see Roche et al. 2006). Because of a reduced immune response, negative energy status can dramatically delay this process, jeopardizing future fertility (Wathes et al. 2007).

Apart from interest in the consequences of NEB and associated endocrine and metabolic imbalances, there is a growing focus towards the effect of milk yield-promoting diets that are rich in energy and protein (for review, see Leroy et al. 2007). From these studies we can learn that optimum nutritional conditions for follicle growth and ovulation are not compatible with embryo survival and maintenance of pregnancy (O’Callaghan and Boland 1999).

Finally, heat stress can cause a reduction in dry matter intake which prolongs the period of NEB, decreasing plasma concentrations of insulin, glucose and IGF-I, while increasing GH and NEFA (Drew 1999; Butler 2001). In addition, there is a direct effect of heat stress on FSH (increased) and oestradiol (decreased) plasma concentrations (Wolfenson et al. 1997; Wilson et al. 1998). This causes not only poor expression of oestrus, but also delayed follicle selection and thus has potentially adverse effects on oocyte quality (Roth et al. 2001a,b). Heat stress may furthermore increase uterine temperature by decreasing blood flow to the uterus. These changes inhibit embryonic development (Rivera and Hansen 2001), increase early embryonic loss and reduce the proportion of successful inseminations (Garcia-Ispierto et al. 2007). The impact of this heat effect decreases as the embryo develops (Paula-Lopes et al. 2003).

All the factors described above, potentially affecting fertility, are diagrammatically presented in Fig. 1.

Some Clues to Modify the Somatotropic Axis in Order to Generate Acceptable Fertility Results

Tackling the multifactorial problem of subfertility in dairy cows is a real challenge as the ‘skewed somatotropic axis’ described above is not the only reason for the decline in fertility. Evolving farm systems, growing herd sizes, increased managerial demands combined with a reduced labour input per animal and increased susceptibility to diseases, all interfere with the ability of the dairy cow to be successfully bred (Mallard et al. 1998). All these factors should be carefully addressed when formulating management advice to the dairy farm manager, but this is beyond the scope of the present paper.

Metabolic disorders (hypocalcaemia, ketosis and acidosis) and infectious diseases during the puerperium are all key risk factors for efficient reproductive performance (Grohn and Rajala-Schultz 2000; Santos et al. 2004b). Balanced and sophisticated birth management combined with strict follow-up of cow health status early postpartum is vital to prevent a drop in the animal’s appetite. Accurate and repeated assessment of BCS to estimate changes in body reserves is critical. Minimizing BCS changes and thus the ‘exhaustion of the energy reserves’ early postpartum requires an optimal dietary strategy by reducing energy intake during the first weeks of the dry period then an increased energy supply (carbohydrates) shortly pre-partum (for review, see Overton and Waldron 2004). Yet, the beneficial effect of extra pre-partum energy on postpartum energy balance is a matter of debate (Grummer 2007). Furthermore, adequate dietary modulations during the demanding early postpartum period are a promising approach although difficult to achieve (Grummer 2007). Therefore, Van Knegsel et al. (2007a) fed on an isocaloric and isonitrogenous basis, a mainly glucogenic (by-pass starch) or a mainly lipogenic diet (beetpulp, MEGALAC and palm oil) and showed that the glucogenic (or ‘insulinogenic’) diet, stimulates energy partitioning towards body reserves in early lactation. Cows fed the glucogenic diet had lower NEB and reduced body fat mobilization, which led to milk fat depression and less energy partitioned to milk (Van Knegsel et al. 2007b). In a follow-up study (Van Knegsel et al. 2007b), multiparous cows fed with glucogenic diet also had higher plasma insulin concentrations and tended to resume ovarian activity earlier (20.4 ± 2.1 days) compared to cows fed with more lipogenic diet (26.1 ± 2.1 days).

© 2008 The Authors. Journal compilation © 2008 Blackwell Verlag
It is speculated that changes in management are more likely to have a positive effect on EB. Shortening or even skipping the dry period improves dry matter intake peripartum, reduces milk production in early lactation, improves energy balance and reduces the number of days postpartum till resumption of ovarian activity (Gumen et al. 2005; Rastani et al. 2005).

Besides this, growing attention is being paid to dietary fatty acid content and composition provided by supplemented by-pass fats during the early postpartum period. Not the effect on energy balance as such but improved steroid secretion and alteration of the fatty acid profile (more ω-3 poly-unsaturated fatty acids), resulting in modified prostaglandin metabolism (Thatcher et al. 2006). Suppression of milk fat synthesis by supplementation of rumen-protected conjugated linoleic acids (trans-10, cis-12) has been suggested to restrict energy loss through milk (Castaneda-Gutierrez et al. 2005).

Yet, in spite of several recent interesting papers, the outcome on energy balance and fertility are equivocal. An extensive description and clear overview of nutritional strategies supporting the metabolic demands during the transition period are given by Overton and Waldron (2004) and are beyond the scope of the present paper.

Finally, genetic selection programmes in the dairy industry have emphasized milk production traits by unintended mobilization of cow body reserves. This loss in BCS is not only dependent on the available mass of adipose tissue but also on a genetically determined set-point for BCS. This set-point is correlated with reproductive outcome (Lucy 2007). Therefore, not only fertility traits as such (Royal et al. 2000), but also variables comprising changes in BCS early postpartum should be included in genetic selection criteria.

Conclusions

Intense selection for milk production has resulted in an immense priority for the high-producing dairy cow to partition energy to milk, at the cost of body reserves. This has resulted in excessive NEB and poor reproductive performance. Thus, milk production and reproductive performance have conflicting interests in high-producing dairy cows. Metabolites and metabolic hormones associated with energy prioritizing for milk production (NEFA, insulin, glucose, IGF-1, β-OH) influence fertility, indirectly by modulating the somatotropic/gonadotropic axis, as well as directly at the ovary, follicle or uterine environment. Strict follow-up peripartum to monitor health and BCS loss and direct treatment of infectious or metabolic disorders in early lactation will limit fertility disorders postpartum. Furthermore, a series of promising management, genetic selection and nutritional strategies have been proposed, which have the potential to shift the somatotropic axis prioritizing energy partitioning of milk to a somatotropic axis with an increased priority for body reserves to improve fertility. Yet, research in this area is limited. Exploring such strategies, comparing their benefit or even combining two or more strategies is an extremely interesting area of research, and essential to improve health and welfare of the modern dairy cow.

References


Nutrient Prioritization and Fertility in Dairy Cows

101


Maedler K, Spinas GA, Dyntar D, Moritz W, Kaiser N, Donath MY, 2001: Distinct effects of saturated and mono-
unsaturated fatty acids on beta-cell turnover and function. Diabetes 50, 69–76.


Spicer LJ, Chamberlain CS, Francisco CC, 2000: Ovarian action of leptin: effects on insulin-like growth factor-I-


Yaakub H, O’Callaghan D, Boland MP, 1999: Effect of roughage type and concentrate supplementation on follicle numbers and in vitro fertilisation on follicle numbers and in vitro fertilisation and development of oocytes recovered from beef heifers. Anim Reprod Sci 44, 1–12.


Author’s address (for correspondence): J Leroy, Laboratory for Veterinary Physiology, Department of Veterinary Sciences, Faculty of Pharmaceutical, Biomedical and Veterinary Sciences, University of Antwerp, Universiteitsplein 1, Gebouw U, B-2610 Wilrijk, Belgium. E-mail: jo.leroy@ua.ac.be

Conflict of interests: All authors declare no conflict of interests.