Metabolism and Reproduction, the Battle for Nutrients

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Take Home Messages

For several decades, researchers worldwide have reported 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 started focusing on the metabolic and endocrine factors that influence fertility in modern dairy cows. Basically, these numerous and very interesting studies focused on endocrine signalling between the brain and ovary, on follicular growth, on the quality of the corpus luteum and the developmental competence of oocytes and embryos. The basic outline and at the same time, the most important things to remember in the present review paper are:

- Dairy cows selected for high milk yields display an absolute priority for their energy to be partitioned to the milk production process in the udder.
- This severe energy priority is at the cost of the cow's own body reserves and functioning, being recognized as a significant loss in body condition and a higher sensitivity to diseases.
- The degree of body reserve mobilisation, and thus body condition loss, is correlated with poor reproductive performance.
- There is growing scientific evidence that this energy saving and mobilisation status in the dairy cow early postpartum affect fertility negatively at the level of the 1) brain; 2) ovaries; 3) uterus 4) oocyte and embryo quality. These interactions are complex and only the most important and obvious links will be discussed in the present paper.

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- Only attention to management practices around parturition that optimize health, feed intake and body condition loss, and direct treatment of disorders will limit fertility disorders postpartum.

This review paper will focus on two important questions: is there a mismatch between metabolism and fertility, and what can the dairy manager learn from research to tackle the problem of reduced fertility?

Introduction

Disappointing reproductive performance in high producing dairy herds is a global problem, characterized as multifactorial and has prompted a multidisciplinary approach in which animal scientists, veterinarians and molecular biologists are 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. After giving birth, the process of getting pregnant again in dairy cows starts with clearance and involution of the uterus followed by resumption of ovarian activity. This should result in completion of the growth of a healthy ovarian follicle enclosing a competent oocyte, and ultimately in estrus, 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 estrous cycles postpartum leading to prolonged calving to first insemination intervals. In this context, especially instability within the hypothalamo-pituitary-ovarian-uterine axis has been studied thoroughly (Lucy 2001; Butler 2003). The concomitant reduced estrus expression, anestrus, cyst formation and delayed first ovulation have been extensively documented (Lopez et al. 2004; Vanholder et al. 2006a). Secondly, attention has focussed on disappointing conception rates and the increasingly high incidence of early embryonic mortality (Bilodeau-Goeseels and Kastelic 2003). Fertilization of oocytes from high genetic merit cows resulted in significantly lower blastocyst yields in vitro, irrespective of milk production. Embryo quality is also reduced in high producing dairy cows compared with non-lactating counterparts (Leroy et al. 2005a). Up to 70-80% of the total embryonic and fetal losses typically occur during the early embryonic, pre-attachment period which clearly seems to be a very sensitive time frame in early development.

Modern dairy cows, albeit subfertile, produce vast amounts of milk mainly due to significant genetic improvements, combined with nutritional management optimized towards lactation. Based on almost unchanged heifer fertility over the past several decades, it is generally accepted that the reproductive processes of modern dairy cattle are essentially normal when lactation demands are not imposed. Why do modern dairy cows prioritize milk production at the expense of sustained reproductive efficiency? In this review, we aim to answer this question.

▪ From a Biologically Normal Rule to a 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. 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 has yet to be ovulated, fertilized and nourished through an entire gestation. This maternal catabolic mechanism, also genetically programmed, should maximize the chance of survival of the new born offspring. Over the past 40 years, the focus of the dairy industry has been on maximizing milk yield, thereby creating a ‘nutrient highway’ from the daily ration and body reserves 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, resulting in negative energy balance (NEB). Drastically reduced insulin concentrations bring about energy mobilisation and partitioning of energy to the udder. Hypoinsulinemia promotes the production of glucose in the liver (up to 4 kg glucose each day) and acts as a massive trigger to mobilize the fat reserves in the body. The mobilized non-esterified fatty acids (NEFA) serve as an alternative energy source for other tissues to preserve glucose, which is preferentially used by the mammary gland to form lactose. Non-esterified fatty acids are predominantly transported to the liver where they are oxidized to provide energy or transformed into ketone bodies, again an alternative energy source for elsewhere in the body. An aberrant over-load of the liver by NEFA can induce a fat infiltration in the liver and disturbed liver function. Hormone sensitive lipases in adipose tissue of high-yielding dairy cows have an increased sensitivity to lipolytic stimuli (such as low insulin, and high catecholamine or glucocorticoid concentrations, associated with stress). In other words, high yielding dairy cows have been genetically selected to partition even more energy reserves into milk production. 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 at all.

A series of biological mechanisms bring about this 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. 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. In vitro, high NEFA levels have toxic effects on pancreatic cells. 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 due to down-regulation of GH 1A receptors and this can be restored by increasing insulin. 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 glucose production in the liver and fat mobilisation in the fat cells. The resulting high blood NEFA and GH concentrations antagonize insulin action and create a further state of peripheral insulin resistance. So, to conclude, we can say that the low insulin concentrations combined with the reduced insulin sensitivity are necessary to guarantee that even more glucose is conserved to be available for lactose synthesis. Only thanks to this specific (but difficult to understand) metabolic condition is high milk production possible.

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

▪ Interactions between Body Metabolism and Reproductive Functioning

Extensive scientific research has shown that mechanisms that regulate energy and nutrient distribution in the body (the so called “somatotropic axis”) may affect the reproductive system at different levels of the hypothalamo-pituitary-ovarian axis (the so called “gonadotropic axis”) (Chagas et al. 2007). Within the hypothalamus, interactions between the gonadotropic and somatotropic systems may occur in the brain and more specifically in the pre-optic area (Blache et al. 2007). This region produces the releasing hormones that control the secretion of both gonadotropins and somatotropin. In addition, it plays a crucial role in integrating appetite, estrous behaviour and sensing of the nutritional status. 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. 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. There are other metabolic signals that are probably involved although their specific role currently remains unclear.

At the ovarian level, follicular growth and development seem 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. Gong (2002) showed that the beneficial effects of insulin on ovarian function 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-dependant GLUT-4 only plays a supportive role. 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 (Gong 2002). Consequently, low circulating IGF-1 concentrations negatively influence the onset of postpartum ovarian activity and seem to be involved in the development of cystic ovarian follicles. At the ovarian level, NEFA may affect follicular growth and development by acting directly on follicle cells. Adding NEFA 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; Vanholder et al. 2006b).

In conclusion, metabolic changes induced by the somatotropic system to sustain 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 and Embryo Quality

Fertility is more than the optimal functioning of the ovaries resulting in normal estrous cycles, right timing of estrus and ovulation. The quality of the female gamete and that of the embryo are also of paramount importance. 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 preovulatory follicle two to three months later (Britt 1992). The quality of the oocyte can be then jeopardized and we know from descriptive studies that early embryonic death is a major cause of reproductive failure in dairy cows, accounting for up to 80% of pregnancy losses. In the next review paper more attention will be paid to the cause and the importance of this reduced oocyte and embryo quality in the disappointing reproductive outcome.

All the factors described above potentially affecting fertility are diagramatically presented in Figure 1.

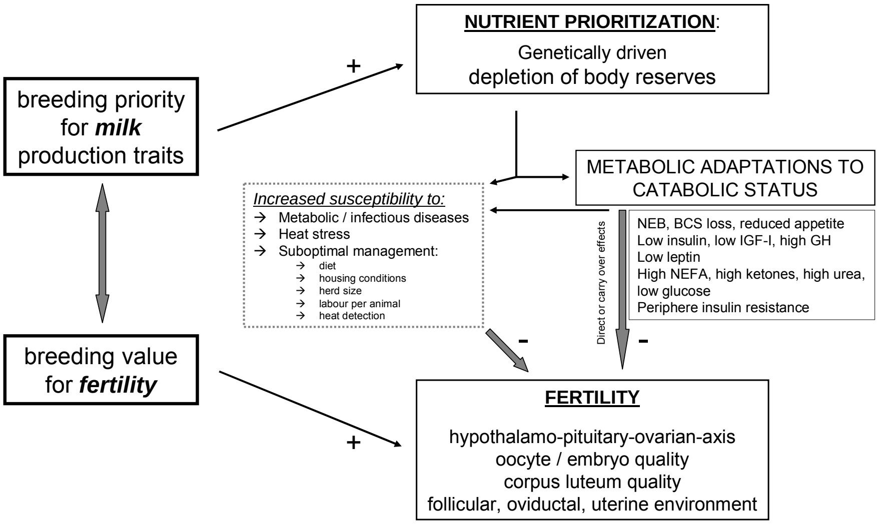

Figure 1. Interaction between genetic selection for milk production and fertility. The imposed metabolic and endocrine changes sustaining milk production in combination with the increased susceptibility to heat stress, diseases and suboptimal management conditions all negatively affect reproductive performance of the high producing dairy cow.

▪ Other Factors Affecting Fertility

Along with genetic selection towards higher milk production, modern dairy cows became more sensitive to heat stress, as their metabolism and thus internal heat production has also significantly increased. It has been observed that heat stress is injurious to reproduction. In addition to its detrimental effects on energy balance, follicular dynamics, and hypothalamus–pituitary–ovarian axis, it has also been suggested that high body temperatures can be directly toxic to the oocyte and the preimplantation embryo (Hansen 2007). Heat stress occurring 20 to 50 days prior to AI can result in drastically reduced conception rates. This indicates that there is a long term effect of heat stress that impacts the ultimate quality of the oocyte to be ovulated several weeks later. Heat stress is also able to induce degeneration of granulosa and theca cells, and thus compromise steroidogenesis. An excellent overview on the effect of heat stress on embryo quality is presented by Hansen (2007).

It is generally accepted that high yielding dairy cows are more vulnerable to attack from metabolic and infectious diseases. Postpartum diseases are even suggested to be a more important risk factor for reproductive failure compared to NEB. Both the incidence and the severity of clinical mastitis are significantly increased in modern dairy cows, probably due to a depressed immune system early after parturition. Not only mastitis in the early postpartum period, but also intramammary infections occurring at the time of AI, are significantly associated with reduced conception rates (Loeffler et al. 1999), and more specifically with higher risks of abortion within the first 90 days. The possible mechanisms involved in the link between infectious diseases and embryonic mortality have been extensively reviewed by Hansen et al. (2004) and are beyond the scope of this paper.

▪ Some Clues to Modify Metabolism Early Postpartum in Order to Generate Acceptable Fertility Results

Numerous studies, described above, provide a growing amount of scientific evidence that cows prioritize milk production over the need to reproduce. Tackling the multifactorial problem of subfertility in dairy cows is however a real challenge for two important reasons. First of all: the typical metabolism in dairy cows early postpartum prioritizing milk production is hard to alter. During the last decades, cows have been selected for high milk production and thus for energy priority for milk. A modern high producing dairy cow will always consider fertility as a “non-priority”. Secondly, the so called “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. All these factors should be carefully addressed when formulating management advice to the dairy farm manager.

Metabolic disorders (hypocalcemia, ketosis and acidosis) and infectious diseases during the postpartum period are all key risk factors for efficient reproductive performance. 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 body condition to estimate changes in body reserves is also critical. Minimizing changes in body condition and thus the 'exhaustion of energy reserves' early postpartum requires an optimal dietary strategy that reduces energy intake during the first weeks of the dry period and then increases energy supply (carbohydrates) shortly before calving (for review: Overton and Waldron 2004). However, the beneficial effect of extra prepartum energy on postpartum EB is a matter of debate (Grummer 2007). Furthermore, adequate dietary modulation during the demanding early postpartum period is a promising approach though difficult to achieve (Grummer 2007). There is growing evidence to assume that especially the glucogenic diets early postpartum seem to be beneficial for energy balance and the onset of ovarian activity. Lipogenic diets have either no effects or a negative effect on energy balance.

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 (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. However, , the outcome of these nutritional strategies 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).

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

Alot of papers have been used to compose this overview. Only the key references are given; however, an extensive list of the references used can be obtained from the first author.

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