Geert Opsomer

Faculty of Veterinary Medicine,
University of Ghent,
Salisburylaan 133,
9820 Merelbeke, Belgium

METABOLIC PROGRAMMING IN DAIRY CATTLE

Abstract

In humans, there is increasing evidence that metabolic diseases occurring in later life arise *in utero* as a result of programming of key endocrine systems during suboptimal intrauterine conditions, which are often associated with fetal growth retardation. The process by which insults during early life lead to permanent changes in tissue structure and function and finally to low birth weight (BW), is known as intrauterine or developmental programming. Because fetal growth depends primarily on the supply of nutrients and oxygen, intrauterine programming of adult phenotype has been attributed most commonly to poor nutrition *in utero*. Also other factors like environmental temperature, oxygen availability and even overnutrition have been shown to have a significant impact on intrauterine growth and development. Since the placenta is the main organ for communication between mother and fetus, it is clear that placental insufficiency invariably affects embryonic development and health in later life. In order to optimize income over costs, dairy farmers inseminate their nulliparous heifers at adolescent age (14 -15 months), and subsequently strive for calving intervals not longer than 380 days. The latter implies that heifers are still growing and multiparous animals are still yielding large quantities of milk while being pregnant. Dairy cows heavily selected for high milk yield, have specific endocrinological characteristics like low peripheral insulin levels and low peripheral insulin sensitivity, both contributing to safeguard glucose for milk production. Backside of this strongly advanced selection for yield, is the high incidence of a wide range of metabolic diseases that furthermore negatively influence both production and fertility of the cows. Besides, modern dairy cattle are ill-famed for their very short life expectancy. Although dairy cows are well fed during gestation to sustain their high yields, they partition lots of nutrients to the udder despite being pregnant. These nutrients are hence withdrawn from both placental and fetal development. Evidence from epidemiological studies is now available demonstrating that milk yield during gestation and environmental factors such as season of pregnancy and parturition influence both the size as well as the intermediary metabolism of the neonatal calf. The latter suggests that further optimization in terms of production, reproduction, general health and longevity in the dairy sector might be feasible by taking into account environmental factors occurring during pregnancy.

Introduction

In humans, there is an explosion of data showing that perturbations like undernutrition during fetal life programs the fetus' metabolism in that sense that survival in the short-term is maximized, but the risk to suffer from a diverse range of health problems in later life is significantly increased. The fetal origins of health and disease hypothesis proposes that adult disease originates through fetal adaptations to intra-uterine challenges like undernutrition that impair fetal growth and eventually result in permanent adaptations in endocrine and metabolic processes (Hales and Barker, 1992; Hales and Barker, 2001; McMillen et al., 2008). The process by which early insults at critical stages of development lead to permanent changes in tissue structure and function is known as intrauterine programming (Fowden et al., 2006). Intrauterine programming of postnatal physiological function has been demonstrated experimentally in a number of species using a range of techniques to compromise the intrauterine environment and alter fetal development. Basically, all these studies have demonstrated that the timing, duration and exact nature of the insult during pregnancy are important determinants of the pattern of intrauterine growth and the specific physiological outcomes (Bertram and Hanson, 2001).

Such intrauterine programming is currently occurring in the high producing dairy cow, which evolved from 2000 to 8000 kg milk production per year over a period of 50 years. To maximize milk production, farmers are stimulated to breed their stock at young age in order to have a first calf at 24 months and subsequently have their cows calved with intervals no longer than 385 to 400 days. The latter implies dairy cows to be rather atypical since they have to manage the compatibility of optimal reproductive performance and (early) gestation with continued growth or the production of large quantities of milk. To assure a high level of milk production heifers should be raised to weigh 350-375 kg at 15 months of age, the age at which they should be inseminated in order to allow calving at 24 months (Wathes et al. 2014). A pregnant lactating cow's capacity to care for her embryo is largely determined by the way she partitions nutrients to support embryonic, placental and fetal development together with her own maintenance and milk production (Wathes 2012). Continued growth, production status and energy balance are known to have a significant effect on how nutrients are partitioned. Rather than being an absolute shortage of energy substrates per se, this metabolic priority for growth and lactation (after calving) is known to generate adverse conditions hampering optimal ovarian functioning, follicular growth, oocyte maturation and early embryonic development (Leroy et al. 2008a; Leroy et al. 2008b). We hypothesize that the rather atypical fact that adolescent animals are still significantly growing while being pregnant and adult cows have to partition large quantities of nutrients to the udder during gestation, both have an impact on the prenatal development of the calf and potentially also on the development of its metabolic features jeopardizing its health, fertility and productivity in later life. In the present manuscript we discuss some epidemiological studies in dairy cattle that have recently been carried out in our department and showed evidence to sustain our hypothesis.

Take home…

The focus of human biomedical research into prenatal programming has been on the predisposition to adult-onset diseases, such as hypertension and diabetes. The latter may not seem relevant to the performance and well-being of productive livestock like dairy cattle. However, efficiency of the production of meat, wool and milk, and susceptibility to disease of domestic livestock continues to vary widely among and within similarly managed herds and flocks of relatively uniform genetic background. At least some of this hitherto unexplained variation is suggested to be attributed to carryover effects of metabolic perturbations during different phases of embryonic and fetal development. The best described effects are those on early muscle and adipose tissue development, with putative consequences for the capacity for lean tissue growth, propensity for fattening, and therefore feed efficiency in meat animals, and on prenatal wool follicle development with permanent consequences for quality and quantity of wool production. In livestock, there is increasing evidence that production characteristics are significantly affected by environmental issues like maternal diet during gestation. Also, it seems likely that the growing body of evidence for nutritional modulation of immune function and susceptibility to infectious and parasitic diseases will eventually implicate prenatal predisposing factors.

Conclusively, animal scientists can learn much from modern studies in human medicine, especially those dealing with the propensity for obesity and incidence of related metabolic diseases. Clearly however, much remains to be learned about molecular and physiological mechanisms of prenatal programming in mammals as well as the quantitative importance of this phenomenon relative to the modulating effects of postnatal nutrition and other environmental factors. From a practical point of view, in terms of animal production, higher knowledge about the underlying mechanisms will allow the incorporation of concepts of prenatal programming into management systems with the ultimate goal of improving food production and eventually farm profitability. Epigenetics and its application into developmental programming set as relatively innovative sciences and their application in the field are thought to bring significant extra value in animal production and might in this respect be seen as an important aid in an attempt to reduce famine in certain areas of our planet.

Since farmers are stimulated to maximize daily growth in their growing young stock in order to maximize milk production in the first and subsequent lactations, they accentuate the mismatch between the milieu the offspring is prepared for and the milieu the neonates actually arrive in, which may lead to even more deleterious effects. Examples hereof are well known in human medicine, where it has been shown that babies that had experienced intrauterine growth retardation and thereafter experience a catch up growth, are more prone to reproductive disorders such as polycystic ovarian syndrome (Ibánez et al. 2008). Epidemiological studies both in beef (Funston and Deutscher 2004; Funston et al. 2012) as well as in dairy cattle (Brickell et al. 2009; Swali and Wathes 2007) have indeed shown that heifers growing fast in the first months of life, have a significantly earlier pubarche but need more inseminations to become pregnant, ending up with a similar age at first calving in comparison with their slower growing peers. In this light, we may refer to the "thrifty phenotype hypothesis", which proposes that the epidemiological associations between poor fetal and infant growth and the subsequent development of type 2 diabetes and the metabolic syndrome result from the effects of poor nutrition in early life, which produces permanent changes in glucose-insulin metabolism (Hales and Barker 2001). This hypothesis may also apply to high producing dairy cattle and might contribute in the high occurrence of metabolic and fertility problems currently mentioned in high yielding dairy cows.

List of references is available on request.