Prenatal programming refers to the fact that insults during pre- and early postnatal life can have long-term consequences on the health and performance. In dairy cattle, physiological conditions, such as maternal body growth, milk yield and parity, and environmental conditions during gestation can create a suboptimal environment for the developing fetus. As a consequence, adaptations of the placental and newborn phenotype take place. In addition, potential long-term effects of prenatal programming influence body growth, fertility, milk yield and longevity in dairy cows. These results suggest that the current management systems may pose a risk for the long-term health and performance of dairy cattle. Hence, in management practices, all pre- and postnatal aspects should carefully be considered in order to raise healthier and more productive dairy cows.

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INTRODUCTION

The primary goal of a dairy farmer is to have his cows produce as much milk as possible, without having disastrous effects on their fertility, health and longevity. In the early 1900s, the first steps were taken to increase productivity in dairy cows by recording the milk yields of cows and registering pedigrees. The primary aim was to breed towards genetically improved livestock. Since then, a rapid evolution in genetic selection towards high milk yield has taken place (Weigel et al., 2017). However, heifers with a genetic potential for high milk yield do not always turn out to be the highest yielding cows, as the phenotype is a result of both genotype and environment. Hence, the impact of management on the performance of cows has gained interest. In this respect, more and more attention has been paid to rearing strategies, to enable genetically valuable heifers to live up to the expectations. Recently, studies have demonstrated that the prenatal life of calves is important, as prenatal conditions can play a role in the ‘developmental programming’ of later health and performance (Astiz et al., 2014; Pinedo and De Vries, 2017).

‘Developmental programming’ refers to the fact that insults during early life can cause specific adaptations in the tissues and metabolism of an organism, which ‘program’ its further growth and development. However, the specific physiological outcome is determined by the timing, duration and exact nature of the insult (Bertram and Hanson, 2001). Environmental factors are believed to have a larger impact when they

SAMENVATTING

Prenatale programmering verwijst naar het feit dat invloeden tijdens het pre- en vroeg-postnatale leven gevolgen kunnen hebben voor de gezondheid en de prestaties op lange termijn. Fysiologische processen bij melkvee, zoals maternale groei, melkgift en pariteit, en omgevingsinvloeden tijdens de dracht kunnen een suboptimale omgeving creëren voor de zich ontwikkelende foetus. Deze resulteren in fenotypische aanpassingen van de placenta en van het pasgeboren kalf. Bovendien kan prenatale programmering op lange termijn een effect hebben op de groei, de vruchtbaarheid, de melkgift en de levensduur van melkkoeien. Deze resultaten suggereren dat de huidige managementsystemen een risico kunnen vormen voor de gezondheid en prestaties van melkvee op lange termijn. Daarom moeten de managementpraktijken alle pre- en postnatale aspecten zorgvuldig in overweging nemen om gezondere en productievere melkkoeien te fokken.
take place during critical stages of early development, such as the prenatal and pre-weaning period. Especially prenatal challenges and their effect on fetal development have been studied, usually referred to as ‘intrauterine programming’ (Fowden et al., 2006a).

PRENATAL PROGRAMMING IN HUMANS

In humans, many findings on intrauterine programming originate from records during the Dutch hunger winter of 1944-1945. A German blockade in the Netherlands cut off food supplies, causing famine in a previously well-nourished population. As women continued to conceive and give birth during the famine, the effects of maternal undernutrition during different stages of pregnancy could be studied in their offspring (Roseboom et al., 2011b). Initially, direct effects of prenatal undernutrition were observed: newborn babies were born unusually small and were presented with an increased insulin sensitivity (Bazaes et al., 2003; Roseboom et al., 2011a). These phenotypic alterations are the result of an ‘intrauterine growth restriction’ (IUGR) (Stein et al., 1995; Painter et al., 2005). By lowering its metabolic rate and overall growth, the fetus attempts to enhance its survival during periods of prenatal undernutrition (Kwon and Kim, 2017). Later studies, however, revealed potentially negative consequences of these adaptations on the longer term (Figure 1). The high insulin sensitivity in small infants is often associated with an accelerated postnatal body growth, referred to as ‘catch-up growth’ (Gafni and Baron, 2000; Ibáñez et al., 2006), but also results in early obesity and peripheral insulin resistance (Soto et al., 2003; Ibáñez et al., 2006). Hence, IUGR has been linked with an increased risk of diabetes during later life, but also other health problems like elevated blood pressure, cardiovascular disease and even reproductive disorders (Ibáñez et al., 1998; Roseboom et al., 2001; Ibáñez et al., 2008; Mericq et al., 2017). The aforementioned findings have led to the ‘Developmental Origin of Health and Disease (DOHaD)’ hypothesis (Hales et al., 1991), stating that besides genotype, the prenatal and early postnatal environment influences the development of chronic diseases.

More recently, studies in human medicine have shown other prenatal factors – besides maternal nutrition – to affect the performance of the offspring. Generally, prenatal exposure to any condition or challenge that may impact the physical integrity and survival of living organisms – also called ‘stress’ – can induce an adverse intrauterine environment, with implications in

![Figure 1. Causes and consequences of developmental programming in humans.](image-url)
terms of developmental programming (Entringer et al., 2010). In addition to maternal nutrition and physical health, maternal lifestyle, i.e. exercise level, smoking and alcohol consumption, and mental health during pregnancy have been demonstrated to be important for the offspring’s health (Syme et al., 2010; Lewis et al., 2015; Mourtakos et al., 2015; Godfrey et al., 2017). Finally, environmental factors have been demonstrated to contribute to the process of developmental programming. Multiple studies have shown an effect of birth month on disease risk (Vassallo et al., 2010; Ambrosi et al., 2012) and longevity (Flouris et al., 2009; Gavrilov and Gavrilova, 2011), with most researchers agreeing on the fact that people born during autumn have an advantage.

Prenatal programming in dairy cattle

In dairy cows, the optimization of management systems has resulted in an enormous evolution in milk yield during the last fifty years. A lot of attention has been paid to feeding strategies, providing cows with high quality roughages and well-balanced rations. Hence, undernutrition – defined as not having enough food – is a rare or even non-existing phenomenon in modern dairy cattle. However, current management systems do impose a challenge for fetal development. Dairy farmers breed their young stock at a young age in order to have a first calf at a maximum of 24 months. Subsequently, cows are expected to calve at intervals no longer than 385 to 400 days. This implies dairy cows to be rather atypical because they have to manage the compatibility of (early) gestation with continued growth or the production of large quantities of milk. Continued growth and the synthesis and secretion of milk are known to be highly demanding in terms of nutrient needs. Hence, rather than being an absolute shortage of energy substrates per se, this metabolic priority for growth and lactation might generate adverse conditions for the unborn calf, with potential long-term consequences on its postnatal health, performance and longevity.

Continued growth in nulliparous heifers

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 become pregnant in order to allow calving at 24 months (Wathes et al., 2014). As heifers have only reached 55% of their mature size at that time, a large part of their body growth takes place during their first gestation (NRC, 2001). Hence, the normal hierarchy of nutrient partitioning between maternal body growth and fetal growth may be altered (Wallace et al., 2006). In sheep, for example, there is a general consensus that overnutrition during gestation in adolescent ewes gives rise to a lighter progeny, while the dam generally experiences a significant increase in body condition. In this paradigm, rapid maternal growth results in placental growth restriction and often premature delivery of low birth weight lambs (Wallace et al., 2006). As dairy farmers are currently stimulated to maximize daily growth in their young stock, the rapid growth in pregnant dairy heifers is believed to create a similar condition as in adolescent sheep, with consequences for the developing placenta and fetus.

High milk yield in multiparous cows

In multiparous cows, heavily selected for milk production, the lactating mammary gland has a much higher requirement for nutrients than the gravid uterus (Bauman and Currie, 1980). Hence, lactation during gestation leads to a significant ‘loss’ of nutrients (like proteins and glucose) for the fetus, because these are diverted towards the udder instead of the gravid uterus. Kamal et al. (2014) described that dairy cows, on average, produce 6,193 kg milk during their 278-day gestation. This implies that the calf developing in utero in the lactating cow, ‘misses’ in total 446 kg glucose (on average 72 g glucose per kg milk produced) and 217 kg proteins compared with a calf developing in a non-lactating dam. However, high milk production per se is not expected to be the only cause of negative effects on the developing fetus. The actual energy status of the dam, being the final result of the cow’s body condition score, level of dry matter intake and milk production, might even be a more important influencing factor (Senosy et al., 2012; Kamal et al., 2014).

Consequences of prenatal programming in dairy cattle

Recent studies have described both short- and long-term effects of prenatal programming in dairy cattle, which are elaborated below.

Placenta and newborn calf

In placental mammals, a functional placenta is crucial for the development of the fetus, as it is the organ through which respiratory gases, nutrients and wastes are exchanged between the maternal and fetal systems. In ruminants, a cotyledonary placenta is seen. The placenta and newborn calf
al., 2006b; Fowden and Moore, 2012). In a previous study by the authors on fetal membranes in Holstein Friesian (HF) and Belgian Blue (BB) cattle, parity of the dam and birth season were revealed to affect the placental phenotype (Van Eetvelde et al., 2016). More specifically, two adaptive mechanisms are seen, i.e. an increase in number of cotyledons (in growing BB dams) and an increase in cotyledonary surface (in lactating HF cows and summer placentas). Studies in sheep have shown similar results, with a larger cotyledon number (Heasman et al., 1999) and an increasing proportion of fetal tissue (Steyn et al., 2001) in placentas of nutrient-restricted ewes. This indicates that maternal body growth, maternal milk yield and high ambient temperatures create a ‘stress’-situation for the developing conceptus, comparable to nutrient restriction. As a consequence, the placenta adapts its phenotype in order to maintain fetal growth (Steyn et al., 2001).

Along with the placental adaptations, prenatal influencers have been shown to induce phenotypic adaptations in newborn dairy calves. High ambient temperatures and high maternal milk yield during gestation have been associated with a reduced birth weight (Kamal et al., 2014). In dairy cattle, low birth weights have been described to be one of the risk factors for an increased incidence of unexplained stillbirth (Berglund et al., 2003; Windeyer et al., 2014). Hence, calves born during hotter months and/or born out of high-yielding cows might be at a higher risk for early morbidity and mortality. Moreover, shorter dry periods have also been associated with the birth of smaller calves (Kamal et al., 2014). This indicates that especially in cows selected for great milk yield and high persistency – resulting in a shorter dry period – a further negative effect on the developing fetus is expected, with potential repercussions for their survival and health. In addition to the reduced birth weights, lower insulin levels are seen in calves born during summer, indicating an increased insulin sensitivity (Kamal et al., 2015; Van Eetvelde et al. 2017). Furthermore, the insulin levels at birth have been shown to be negatively associated with ambient temperatures at the end of gestation (Van Eetvelde et al., 2017) (Figure 2). Similar results have also been described in crossbreeding studies in horses. While ‘restricted’ foals have lower insulin levels, higher insulin levels are seen in ‘overgrown’ foals (Forhead et al., 2004; Peugnet et al., 2014).

Hence, it can concluded that challenges in terms of nutrient supply to the fetus (increase or decrease) lead to adaptations not only to the placenta but also to the phenotype of the neonatus and its metabolism. However, the underlying mechanism of these metabolic alterations remains largely unknown. Furthermore, especially in cattle and horses, it is not clear yet whether and how these metabolic adaptations persist in later life and could be responsible for adverse outcomes on the long term.

Figure 2. Relation between glucose and insulin levels and the environmental temperature at birth. The left axis presents the average glucose (mMol/L) and insulin (mU/L) levels of the calves by the month of birth. On the right axis, the average ambient temperature at the birth month is shown. Despite similar glucose concentrations, insulin concentrations were significantly negatively correlated with temperature at birth (Van Eetvelde et al., 2017).
Catch-up growth, adiposity and fertility

While body growth in calves is largely dependent on the feeding strategy, it is also related to birth weight. When fed a conventional limited diet, a moderate growth rate of calves (independent of the calves’ birth weight) has been described, preventing low-weight calves to catch-up with their high-weight counterparts (Swali and Wathes, 2006; Brickell et al., 2009b). However, when ad-libitum feeding is applied, a significant increase in body weight is seen compared to limited fed calves (Maccari et al., 2015). Furthermore, when applying high feed levels, e.g. by automatic milk-feeding, a negative association between size at birth and growth rate during the first months of life has been reported (Lundborg et al., 2003; Svensson and Liberg, 2006). This implies that in the smallest calves, which have suffered from IUGR, a compensatory growth or ‘catch-up growth’ is seen, which is further accentuated when high milk regimes are applied. Although this rapid postnatal growth might seem beneficial, it has been shown to result in a higher accretion of fat than lean mass (Ford et al., 2007). This might be explained by the fact that the number of muscle fibers is set at birth and cannot increase postnatally (Greenwood et al., 2000). Hence, when suboptimal prenatal conditions have resulted in a reduced intrauterine muscle development, this is very likely to have consequences on the long-term body growth (Long et al., 2009). Zhu et al. (2006) showed a reduced muscle mass and altered muscle fiber distribution in the offspring of nutrient-restricted ewes, resulting in a reduced lean tissue growth and predisposition for adiposity during early life (Greenwood et al., 2000). In dairy cattle, catch-up growth has been shown to result in a slightly higher body weight at calving, but mainly a larger weight loss after the first parturition (Swali and Wathes, 2007). This may indicate a greater degree of body tissue mobilization, with a potentially increased risk of metabolic disorders around parturition (De Koster and Opsomer, 2013). In addition, fast-growing heifers, despite being younger at first breeding, have been shown to need more inseminations to become pregnant (Brickell et al., 2009a). These results show remarkable similarities with human studies on IUGR children, associating a small birth size and rapid postnatal growth with increased adiposity and negative effects on later fertility and health (de Zegher et al., 2017).

Whether intrauterine programming results in a positive or a negative outcome, is believed to be largely determined by the ‘match’ or ‘mismatch’ between the

![Figure 3. Hypothetical model on how the interaction between the pre- and postnatal environment may affect the phenotype of dairy cattle. If the pre- and postnatal environment match, the fetal adaptations are hypothesized to enhance the performance of the cow. In contrast, a mismatch between the pre- and postnatal environment might have detrimental effects on health, fertility and lifespan (Van Eetvelde and Opsomer, 2017).]
intrauterine and postnatal environment. The ‘thrifty phenotype hypothesis’ states that a poor prenatal environment (due to maternal undernutrition or other ‘stress’ factors) can induce permanent changes in the metabolism of the fetus, preparing it for similar conditions after birth (Hales and Barker, 2001). When restricted feeding is applied postnatally, hence creating a ‘match’ with the prenatal environment, the offspring benefits from its adapted phenotype. However, when there is an abundance of nutrients in the postnatal life, a ‘mismatch’ between the pre- and postnatal life may develop, with potential detrimental consequences for the calf’s future health and performance (Figure 3). However, in the majority of the cases, it is difficult to distinguish the specific effects of the pre- versus postnatal environment. Especially the effect of a rapid postnatal growth per se (irrespective of birth weight) on the adult phenotype is difficult to assess, as it is in most cases preceded by a reduced prenatal growth (Jimenez-Chillaron and Patti, 2007). Studies in mice however, have provided evidence for the fact that early postnatal catch-up growth is the key risk factor for metabolic problems during later life: while mice with a low birth weight exhibiting postnatal catch-up growth had a higher risk to develop obesity and diabetes, prevention of postnatal catch-up growth increased metabolic health and lifespan (Bieswal et al., 2006). Hence, the accelerated growth often observed after IUGR may be more detrimental than the intrauterine adaptations per se (Singhal and Lucas, 2004). Indeed, human studies have shown that a lower nutrient intake and slower growth early in postnatal life (irrespective of birth size) have beneficial effects on later health (Singhal et al., 2003).

Based on the striking similarities between results of studies done in dairy cattle and those reported in human medicine, the human “thrifty phenotype” model (Hales and Barker, 2001), should stimulate to critically assess the potential long-term consequences of the currently applied management system. As heifer rearing is a major cost for a dairy farmer, the aim is to shorten the non-productive life of a heifer by increasing early body growth and thus decreasing age at first calving (Ettema and Santos, 2004; Bach and Ahedo, 2008). As early body weight accretion is most efficient (Bach and Ahedo, 2008), dairy farmers have been stimulated to maximize the growth of their calves during the first months of life, especially during the pre-weaning period. Furthermore, enhanced liquid feeding has shown promising results on short-term performance, in particular on milk yield during first lactation (Shamay et al., 2005; Moallem et al., 2010). However, little is known about the long-term effects of this ‘accelerated feeding’ on later fertility, metabolic health and lifespan. Following the ‘thrifty phenotype hypothesis’, the enhanced liquid feeding as currently used in pre-weaned calves, might accentuate the mismatch between the environment for which the offspring is prepared and the one in which it is actually born, which may have long-term deleterious consequences.

**Milk yield and longevity**

Studies on the performance of dairy cattle have revealed that, besides age and weight of the heifer at first parturition, multiple prenatal factors are associated with the amount of milk produced during first lactation. Most studies agree on the fact that a higher parity of the dam is associated with a reduced performance of the daughter. Older dams have been shown to produce offspring with a lower milk yield during their first, second and third lactations (Banos et al., 2007; Berry et al., 2008; González-Recio et al., 2012; Van Eetvelde et al., 2020a). Furthermore, maternal milk yield during gestation has been shown to affect offspring longevity, with a reduced lifespan in daughters born out of mothers that were lactating while pregnant (González-Recio et al., 2012). Recently, the authors performed a study on dairy cows that had reached a threshold life time milk production of 100,000 kg. In this study, the authors aimed to find intrinsic cow factors that are associated with the ability to combine a long lifespan with a high functionality. In accordance with previous studies, higher parity of the dam was confirmed to negatively affect the offspring’s performance, as daughters of high-parity cows were less likely to reach a life time milk yield of 100,000 kg (Van Eetvelde et al., 2020b).

Although the aforementioned studies indicate maternal factors to be important for long-term performance of the offspring, it is hard to detach the direct effect of high maternal milk yield from the effect of maternal age/parity in multiparous dairy cows. The higher genetic merit in younger dams might be one of the reasons why they give birth to more productive daughters, but this can hardly be the single cause. After all, genetic improvement in milk yield is considered to be slow (1% of the mean per year (Brotherstone and Goddard, 2005)) and studies were only performed during a limited time period. Hence, the recorded effects of maternal age are larger than can be expected from genetic improvement only (Astiz et al., 2014) and need further exploration. The results on the effect of maternal age seem similar to human studies, showing maternal ageing to be associated with placental dysfunction (Lean et al., 2017) and a reduced fitness of the offspring (Cardwell et al., 2010). However, there is a fundamental difference between late childbearing women and multiparous dairy cows, as these cows conceived their first calf at a young age. Hence, the effect of maternal age needs to be separated from the effect of parity to draw further conclusions. It has been suggested that in multiparous cows, the negative effect on the fetus might be caused by changes in its metabolic environment (Fuerst-Waltl et al., 2004; Astiz et al., 2014). This implies that parity might have a higher impact than age of the dam, as the former represents the previous number of parturitions and thus periods of metabolic stress the cow – and her reproductive organs – have been exposed to. Future research should therefore be focussed on the metabolic health of the
Cow, rather than on her milk yield, age or parity, to identify the underlying mechanism(s) responsible for the programming of the fetus.

In addition to maternal effects, seasonal effects on long-term offspring performance have been described. In dairy cattle, research on the effect of birth month shows conflicting results, not only between studies but also between herds (Soberon et al., 2012; Chester-Jones et al., 2017; Van Eetvelde et al., 2017; Van Eetvelde et al., 2020a). However, a similar trend is seen as in human studies. Cattle born in autumn have higher first-lactation milk yields and are more likely to reach a lifetime milk yield of 100,000 kg (Van Eetvelde et al., 2020a and 2020b). Several reasons for the long-term effect of birth season have been suggested. As described above, high ambient temperatures at the end of gestation have been associated with changes in the phenotype of the calf, such as reduced birth weight and high insulin sensitivity (Kamal et al., 2014; Tao et al., 2014; Kamal et al., 2015). However, whether these changes in metabolism persist during later life and are responsible for the effect on later performance and health, is still unclear. On the other hand, the birth season effect might be related to differences in photoperiod and hence vitamin D status of both the dams and the neonates. In human studies, it has been shown that besides the primary role of vitamin D in calcium and skeletal homeostasis, it plays a more complex role in the modulation of immune function (Hewison, 2012). In cattle, as in other mammals, exposure to sunlight is one of the principal natural mechanisms through which vitamin D is produced. In grazing cattle, seasonal variation in vitamin D levels have been shown, with low levels in winter months (Casas et al., 2015). Even in intensively managed cattle, where a year-round supplementation is applied, low vitamin D levels have been shown in fresh cows, resulting in more than 25% of newborn calves to be vitamin D-deficient (Nelson et al., 2016). Due to minimal ultraviolet light radiation during winter, vitamin D levels are expected to be even lower from March to May (Krzyścin et al., 2011), suggesting spring-born calves to be immunologically deficient in terms of vitamin D levels (Casas et al., 2015). This could induce an increased disease susceptibility in these calves, eventually leading to a lower performance and longevity than in calves born during autumn. Additional research is needed to identify the association between levels of vitamin D in neonatal calves and health and performance in later life. In addition, the need for higher supplementation levels in pregnant cows, especially during winter months, should be assessed.

CONCLUSIONS

Studies in dairy cattle have shown that typical physiological conditions, such as continued body growth and milk yield, and environmental conditions, such as high ambient temperatures during gestation, can create a suboptimal environment for the developing fetus. As a consequence, adaptations in the phenotype of the placenta and the calf are noticed, with potential long-term effects on their growth, milk yield and longevity. This might impose questions about the current management strategies, where we want heifers to calve at an early age and cows to be inseminated very early in lactation. In addition, the current heifer rearing strategies – and especially the enhanced liquid feeding during the pre-weaning period – might impose risks for the future performance, as it accentuates the ‘mismatch’ between the pre- and postnatal environment.

As cows selected for high milk yield are likely to prioritize milk production despite their stressed energy level, it might be difficult to counteract this mismatch by intervening during the prenatal timeframe. However, there may be an opportunity for interventions during early postnatal life in calves, by modulating the catch-up growth and preventing the development of metabolic diseases in later life. Hence, in management practices, all of these aspects to raise healthier and more productive dairy cows that live longer, should carefully be considered.

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**Over dieren**

**Varkens ruiken**

‘ik kijk niet naar ze, want ik wil ze eerst ruiken. Eerst ruiken dan zien is mijn devies. En dan ineens, plotsklaps, een wonder … die heerlijke geur van varkens die in het stro hebben gelegen, bereikt mijn neus. Dat is de essentie van het varkenshouden.’