The Importance of the Periconception Period: Immediate Effects in Cattle Breeding and in Assisted Reproduction Such as Artificial Insemination and Embryo Transfer

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Abstract In livestock breeding, the successful outcome is largely depending on the "periconception environment" which, in a narrow sense, refers to the genital tract, where gametogenesis and embryogenesis occur. During these early stages of development, gametes and embryos are known to be particularly sensitive to alterations in their microenvironment. However, as the microenvironment somehow reflects what is going on in the external world, we must widen our definition of "periconception environment" and refer to all events taking place around the time of conception, including metabolic state and health and nutrition of the dam. In modern dairy cows that have to manage an optimal reproductive performance with continued growth and high milk yield, the periconception period is particularly challenging. The metabolic priority for growth and lactation is known to generate adverse conditions hampering optimal ovarian function, oocyte maturation, and development of embryo/fetus. In addition, by using artificial reproductive technologies (ARTs), gametes and/or embryos of livestock are exposed to unnatural conditions outside the male and female genital tract. Artificial insemination, the most widely used technique, is currently yielding pregnancy rates similar to natural mating, and calves

Focus: Discussing the immediate effects that the periconception environment can have on conception success, the rate of fertility, and the establishment of pregnancy in livestock.

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produced by AI are equally viable after natural mating. In contrast, other ART, such as multiple ovulation and embryo transfer, have been reported to induce changes in gene expression and DNA methylation patterns with potential consequences for development.

Finally, the "periconceptional" environment has been shown to not only influence the successful establishment of pregnancy but also the long-term health and productivity of the offspring. Hence, the optimization of management around the time of conception might open doors to improve animal production and product quality.

Keywords Epigenetics • Artificial insemination • Embryo transfer • Periconception environment • Farm animals

1 Introduction

Livestock breeding is seemingly not very difficult. Unlike in human reproduction, dairy and beef cattle can be selected for fertility traits (Bowley et al. 2015), and animals suffering from suboptimal fertility are eventually removed from the breeding system, unless they are of very high genetic value. However, cattle breeding is nowadays affected by several factors, such as animal management conditions (Shahinfar et al. 2014) and climate change (Burthe et al. 2011; Gauly et al. 2013). These factors can influence or change the "periconception environment." Periconception environment can be interpreted in a broader sense, and all the events that take place during this period are extensively discussed in the various chapters of this book. In the present chapter, we will use the expression "periconception environment" in the narrow sense of the word, first to specifically refer to the male and female genital tract, where gametogenesis and embryogenesis occur. In the second phase, we will also discuss "periconception environment" in a broader sense, when referring to the physiology of the animal and its environment.

At first sight, it may appear that the oocyte, maturing in the ovarian follicle, and the embryo, developing within the oviduct and uterus, are well isolated from issues related to the external environment and therefore obviously benefit from being in a protected environment. However, there is a growing realization that the period during which the oocyte is developing in the ovarian follicle, and also during the first few weeks of embryo development, is one in which gametes and embryos are particularly sensitive to changes occurring in their "protected" environment. Apparently, this "protected environment" somehow reflects what is going on in the external world. Features such as dietary changes; general health issues and inflammation, heat stress, and metabolic stress; and environmental pollution may affect the intrinsic quality of gametes, preimplantation embryos, or even fetal development and

thus negatively impact on conception rates and the chance of a successful establishment of pregnancy in livestock. Furthermore, there is currently more and more evidence, both from studies in humans and in a variety of animal species, that factors influencing the periconception environment not only have consequences on the short term, deteriorating pregnancy results and neonatal survival, but may have a distinct effect on the long term by impairing animal health and productivity later in life. Hence, in livestock there is a considerable interest in this concept, also known as developmental programming, since it may open doors to improve animal production and product quality when implemented in general management strategies (Wu et al. 2006).

However, with the advent of assisted reproductive technologies (ARTs), we must further widen our definition of the periconception environment. "Assisted reproductive technologies" refer to four generations of technologies, which all have an impact on the periconception environment in the broader sense: (1) artificial insemination (AI), (2) multiple ovulation and embryo transfer (MOET), (3) in vitro embryo production (IVP), and (4) cloning and transgenesis (Thibier 2005). In this chapter, we will only focus on the first three, since they are routinely used in practice, whereas cloning and transgenesis are not, although this may soon change with the construction of an animal cloning factory in Tianjin, China (ref http://www.theguardian.com/world/2015/nov/24/worlds-largest-animal-cloning-factory-can-save-species-says-chinese-founder).

By using ART, gametes and/or embryos of livestock are being exposed to unnatural conditions outside the male or female genital tract, such as exposure to ambient air, to changes in temperature and pH, to nonphysiological hormone balances, to synthetic culture media, and even to cryopreservation or to breaches in the cellular membrane. In this chapter, we will reiterate how these changes in periconception environment may affect fertility in livestock and even health of the offspring, with a focus on dairy cattle.

2 Gametogenesis, Embryogenesis, Establishment of Pregnancy, and Fetal and Placental Development in Cattle

Female calves are born with hundreds of thousands of oocytes (Erickson 1966, cited by Britt 2008), which remain in the ovaries as primordial and primary follicles until puberty. The moment of puberty is significantly affected by breed and body growth rates. Furthermore, a cow is a year-round breeder. When heifers start to cycle at about 12 months of age, about every 3 weeks, a single mature oocyte, surrounded by some expanded cumulus cells, is released into the oviduct. The estimated time course of folliculogenesis in the bovine is about 80–100 days (Britt 2008), from the

stage of the primary follicle until the mature Graafian follicle. During this period of oogenesis, follicular waves emerge, but only one dominant follicle is selected to ovulate. Dairy heifers are usually bred at the age of 15 months, just after ovulation.

Bull calves start to produce semen at puberty (9–10 months) and are sexually mature at the age of 2–4 years (Rawlings et al. 2008). In each ejaculate, they produce billions of spermatozoa, and the estimated time course of spermatogenesis is 62 days. Conception rates are high in beef cattle mated by a bull (up to 80%) but significantly lower (40%) in modern high-producing dairy cattle that are currently traditionally bred by AI. In both cases, fertilization of the oocyte occurs within the oviduct. The bovine embryo enters the uterus at about 4–5 days after ovulation, at the early morula stage. During the period preceding embryo attachment, the embryo is free floating and is dependent upon endometrial secretions into the uterine lumen, termed histotroph, both for energy and proteins. The critical period of maternal recognition of pregnancy occurs between days 15 and 18 after ovulation, followed by the initial stages of implantation and early placentation (starting gradually after day 19 (Lonergan and Forde 2015)). In the cow, the placenta attaches to discrete sites of the uterine wall called caruncles. These caruncles are arranged in two dorsal and two ventral rows throughout the length of the uterine horns. The placental membranes attach at these sites via chorionic villi in specific areas called cotyledons. The caruncular-cotyledonary unit is called a placentome and is the functional area of exchanges between the cow and calf. In association with the formation of the placentome, the caruncular area is progressively vascularized to meet the increasing demands of the conceptus. Cattle have been shown to have the synepitheliochorial type of placentation (Wooding and Burton 2008). Fetal survival is dependent upon proper placental growth and vascularity early in pregnancy, while further intrauterine growth is mainly dependent on the placental supply of maternal nutrients and oxygen to the fetus. Therefore, establishment of a functional fetal/placental vascular system is one of the earliest requirements during conceptus development (Vonnahme et al. 2008). However, during pregnancy, the placenta is exposed to a variety of environmental insults which can alter fetal organogenesis and growth, leading to improper pre- and postnatal growth and eventually lower life performance.

Calving rates are typically high in beef cattle after natural mating (80%), and in dairy cattle after artificial insemination (65%) and embryo transfer of in vivo derived embryo (60%), but decrease toward less than 50% after transferring in vitro produced bovine embryos. Interestingly, in the high-producing dairy cow, calving rates after AI have decreased over the last decades to about 40%. In the next paragraphs, we will discuss how these differences can be explained, with an emphasis on dairy cattle.

3 Factors Affecting Periconception Environment Both in Natural Breeding and Assisted Reproduction

3.1 A Dairy Cow Is Not a Typical Cow

To maximize milk production, currently, 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 385–400 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 embryo development (Leroy et al. 2008a, b). In the next paragraph, we will further focus on "reproductive success" in dairy cattle, which can be defined as the ability to produce a healthy offspring in a timely way.

3.2 Physiological Factors Affecting Reproductive Success in Dairy Cattle

3.2.1 Continued Growth in Adolescent Animals

In general, reproductive capacity of nulliparous heifers is higher when compared to that of multiparous animals. While this finding can be attributed to the fact that oocytes and embryos of the nulliparous heifers have not been challenged by the metabolic stress of milk production, one should also not forget the decisive role of the uterus in terms of pregnancy success. Uteri of nulliparous heifers have not been confronted yet with a parturition event which is, in the vast majority of cases, associated with bacterial infection. Besides the better reproductive performance of nulliparous heifers, significant differences have been noted in terms of production, reproductive capacity, longevity, and resilience against metabolic challenges, between offspring of first and higher parity animals (Banos et al. 2007; González-Recio et al. 2012), with, in most cases, the offspring of first parity animals being in a more favorable condition. The latter results may be interpreted as an indication of

the deleterious effects of lactation during conception and early pregnancy since in contrast to multiparous dairy cows, first-parity animals do not lactate.

All too often, however, researchers have used first-parity heifers as non-lactating and hence "negative" controls when examining the effect of lactation and its concomitant metabolic consequences on the animal's reproductive capacity. However, when reproduction has to coincide with continued growth of the first-parity dam, the fetus may face intense competition for nutrients from its mother's own metabolic needs while still growing. 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 nowadays 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 when compared with moderately nourished ewes of equivalent age (Wallace et al. 2006).

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 for which the offspring is prepared and the milieu the neonates actually experience, 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) and 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 the epidemiological associations between poor fetal and infant growth and the subsequent development of type 2 diabetes and metabolic syndrome. Both of these outcomes 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.

3.2.2 High Milk Yield and the Concomitant Metabolic Stress in Lactating Animals

The genetic drive to produce large quantities of milk makes modern dairy cows more vulnerable to factors generally known to impair overall health and fertility. Hence, since dairy cows are challenged by such a variety of environmental factors during the period when they should also reproduce, they represent a "natural" model to describe the effects of periconception environmental challenges on their reproductive capacity. Furthermore, the modern dairy cows' reproductive capacity is

under extreme pressure especially because of very high rates of (early) embryonic mortality (Wiltbank et al. 2016). The latter might be a reflection of the high number of insults the gametes and early embryos are confronted with during the periconception period (Ribeiro et al. 2016; Leroy et al. 2015).

Modern dairy cows have been predominantly selected for high milk yield in early lactation, which is associated with a very high capacity to mobilize body reserves during this period. Calculations have shown that cows can produce as much as between 120 and 550 kg of milk from body reserves on the basis of energy (average 324 kg). Most cows can cope with this metabolic load, which is defined as "the total energy burden imposed by the synthesis and secretion of milk, which is met by mobilization of body reserves." Metabolic load has, however, been opposed to metabolic stress, which is defined as "the amount of metabolic load that cannot be sustained by body mobilization, leading to the down-regulation of some energetic processes, including those that maintain general health" (Knight et al. 2000). Hence, the "over"-mobilization of body reserves during the period of negative energy balance is a key factor for disease susceptibility in modern dairy cattle. The genetically and hormonally driven body mobilization is further significantly aggravated by the mismatch between the energy need and the cow's capacity to take in energy, the latter often being even further negatively affected by an inadequate adaptation of both the gastrointestinal tract and the overall intermediary metabolism. Maximal feed intake in dairy cows occurs commonly at 6–8 weeks in lactation, which is much later than peak production, causing cows typically to be in negative energy balance for 5–7 weeks postpartum (Tamminga et al. 1997). High milk production per se is not the primary cause to elicit negative effects on health and fertility traits, since the effect mainly seems to depend on the overall farm management and production environment.

Typically, the negative energy balance and concomitant body fat mobilization are characterized by specific alterations in peripheral plasma metabolite concentrations such as high non-esterified fatty acids (NEFAs), low glucose and insulin, and high levels of ketone bodies. In our laboratory, ovum pickup (OPU) has been used to demonstrate that these alterations not only occur in the peripheral circulation but are also reflected in the follicular fluid of the ovaries (Leroy et al. 2004). Applying OPU allowed us to get a better insight into the environment in which both the follicular cells and the oocyte have to mature. The effects of the elevated/lowered concentrations of metabolites associated with high milk yield on follicular cells (Vanholder et al. 2005b, 2006) and oocytes (Leroy et al. 2005, 2006) were subsequently evaluated in the laboratory. Main conclusions were that saturated NEFAs at concentrations found in vivo were able to impair proliferation of granulosa and theca cells (Vanholder et al. 2005b, 2006), while oocytes that had to mature in media in which elevated levels of saturated NEFAs were added were associated with lower fertilization and blastocyst rates (Leroy et al. 2005). Furthermore, when oocytes were matured in vitro in media mimicking ketotic situations, low glucose rather than high levels of ketone bodies seemed to be detrimental for subsequent fertilization and blastocyst formation (Leroy et al. 2006, 2008c).

Based on the above, it is clear that the periconception microenvironment of the oocyte affects its developmental competence and thus the subsequent pregnancy success. Whether it can also induce pertinent changes in the offspring's metabolism and body functions, and hence has an effect on its health later in life, is still a matter of debate. Farmers can influence this periconception environment by adequate measures (such as nutrition, health programs, and breeding technologies), as reviewed by Santos et al. (2010). It has been demonstrated that the altered microenvironment gives rise to altered patterns of gene expression in the offspring (Lillycrop and Burdge 2012). Epigenetic phenomena such as DNA methylation or histone modification are crucial in the regulation of gene expression, and intense epigenetic modifications have been shown to take place at a very high rate both in germ cells and in the preimplantation embryo. However, the question still remains whether the abovementioned changes, such as high NEFA levels, which affect the microenvironment of the oocyte and later of the young embryo, can elicit epigenetic changes like DNA methylation or histone modifications.

3.3 Nutrition

In dairy cattle, the potential influence of nutrition on the periconception environment of the gamete and young embryo can be evaluated at three different levels: undernutrition, overnutrition, and diet composition.

3.3.1 Undernutrition

In modern dairy cows, undernutrition as such should be considered as a very rare or even nonexistent phenomenon, since animals that are to be inseminated (both nulliparous heifers and lactating multiparous cows) are generally fed according to their requirements. In beef cattle held under extensive conditions, undernutrition may, however, still occur, especially in specific seasons when animals are outdoors and the development of crops and grass is far below what is needed for animal feeding. Therefore, in lactating dairy cows, undernutrition is mainly regarded as incompetence to cope with the negative energy balance (NEBAL) during the immediate postpartum period. As mentioned earlier, the main challenge for the cows at that time is to optimize their dry matter intake in order to let the NEBAL not become too serious nor to last exceptionally long. As outlined by LeBlanc (2010) and (Mulligan et al. 2006), an inadequate management is the main underlying reason why cows fail to handle the NEBAL and finally experience severe metabolic stress. All too often, the latter leads to subclinical metabolic disease like subclinical ketosis or eventually even clinical ketosis and fatty liver.

Undernutrition in the postpartum dairy cow should therefore be seen as insufficient dry matter intake leading to inabilities for the cows to cope with NEBAL. In terms of reproduction, the latter will first of all be accompanied by a delayed

resumption of normal ovarian cyclicity. Modern high-yielding dairy cows that do experience NEBAL have been shown to resume ovarian activity significantly later in comparison to cows in which the NEBAL was lower. Furthermore, significantly, more ovarian disturbances have been demonstrated in modern high-yielding dairy cows (Opsomer et al. 1998, 2000). In addition, the expression of heat symptoms has been shown to be significantly lower in those cows. The latter often necessitates farmers to inseminate cows based on secondary heat symptoms (such as restlessness and a decreased feed intake and milk yield), which are known to be associated with lower pregnancy results.

Most dairy cows develop the first postpartum dominant follicle approximately within 2 weeks after calving, but only about 40% of these follicles produce sufficient estradiol to stimulate ovulation, despite having normal ultrasound appearance and growth (Cheong et al. 2015). The mechanism leading to a correctly timed ovulation of a fertile oocyte is based on well-orchestrated cross talk within the hypothalamic-pituitary-ovarian axis (Cheong et al. 2015). In dairy cows selected for a high level of milk production, peripheral levels of glucose, insulin, and insulin-like growth factor-1 (IGF-1) are known to be substantially reduced (Marett et al. 2015; Bossaert et al. 2008). Lower peripheral insulin levels have been associated with non-ovulation of the dominant follicle, finally giving rise to cystic ovarian disease (Vanholder et al. 2005a). The underlying reason has shown to involve compromised theca cell function, finally leading to estradiol levels that are inadequate to provoke an ovulatory LH peak and hence ovulation. The reason for the compromised theca cell function has been attributed to the elevated levels of non-esterified fatty acids concomitant with overall fat mobilization (Vanholder et al. 2005b, 2006), although not all authors support this hypothesis. Overall, Cheong et al. (2015) recently concluded that cows that fail to ovulate the first postpartum dominant follicle are characterized by lower periparturient energy balance, increased insulin resistance, lower LH pulsatility, and lower intrafollicular concentrations of androstenedione and estradiol.

Undernutrition or, particularly for the dairy cow, insufficient dry matter intake and thus a more extensive NEBAL may cause adverse changes of metabolites in the ovarian follicular fluid. Although altered metabolite concentrations give rise to lower oocyte quality and hence lower fertilization rates as outlined above, this is less important for embryo growth because of the limited nutrient requirements of the early embryo and fetus for growth and development during the complete first half of gestation. It is furthermore well known that 75% of the growth of the ruminant fetus occurs during the last 2 months of gestation (Robinson et al. 1977). However, it is during the early phase of fetal development that maximal placental development and growth, differentiation, and vascularization occur, as well as fetal organogenesis, all of which being critical events for normal conceptus development. Nutrient restriction for the fetus is broadly defined as any series of events that reduce fetal and/or perinatal nutrient supply during critical windows of development. Basically, nutrient restriction can result from altered maternal nutrient supply, placental insufficiency, deranged metabolism and regulation, physiological extremes, and environmental conditions. From a practical standpoint, maternal nutrient supply

and environmental conditions leading to stress responses are the most likely observed causes of nutrient restriction in ruminant livestock (Reynolds et al. 2006).

3.3.2 Overnutrition

Excessive energy intake particularly from high carbohydrate diets in cattle can reduce fertilization and embryo quality in some, but not all, circumstances. The latter has been attributed to increased circulating insulin levels during the final week of follicle growth, although the underlying mechanisms are still not clear (Wiltbank et al. 2014). Adamiak et al. (2005) demonstrated that high feeding levels were beneficial to nulliparous heifers in low body condition, but detrimental to oocytes from animals of moderately high body condition. Also here, elevated levels of insulin were considered as the underlying reason for this negative influence. Later, these findings were confirmed by Rooke et al. (2009) by feeding heifers diets high in starch, although they were able to avoid the adverse effects on oocyte quality when leucine intake was increased.

3.3.3 Composition of the Diet

Management strategies for transition cows (i.e., 3 weeks before calving until 2 weeks after calving) are mainly focused on helping the cows to cope with the metabolic load by optimizing health, minimizing stress (e.g., by minimizing the changes in group or ration), and stimulating dry matter intake and immune function. These are great opportunities for the veterinary practitioner to regularly monitor and adapt the herd management (Mulligan et al. 2006; LeBlanc 2010). A relatively new approach is to implement rather short-term changes in the quantity or composition of the diet at key stages in the reproductive process. Therefore, the term focus feeding, which refers to implementing short periods of nutritional supplements that are precisely timed and specifically designed to ameliorate the reproductive process including embryonic and fetal growth and development, has been introduced (Martin and Kadokawa 2006). In this context, Wiltbank et al. (2014) discussed possibilities to supplement rumen-protected fats in the ration of dairy cows. Of special interest herein is the supplementation of methionine since this is a rate-limiting amino acid for milk production and is known to be a methyl donor, which may potentially affect the status of DNA methylation and hence the expression level of certain genes.

Furthermore, application of diets specifically designed to improve fertility by counteracting mechanisms related to the NEBAL or by supporting a specific pathway necessary for successful fertility has always been a very attractive way to circumvent the impairment of reproduction during early lactation. Although the reproductive system is known to be influenced by multiple hormones that are also involved in the adaptation toward high milk production (growth hormone, IGF-1 and leptin), only insulin is known to be relatively sensible to the composition of the

ration. Ovarian follicles have been shown to bear insulin receptors (Bossaert et al. 2010), and cows with lower peripheral insulin levels in the immediate postpartum period have been demonstrated to suffer from delayed postpartum ovarian resumption and are at higher risk to suffer from cystic ovarian disease (Vanholder et al. 2005a). Therefore, glucogenic diets have been advocated in the immediate postpartum period aiming to enhance the peripheral insulin concentrations and advance normal ovarian resumption (Gong et al. 2002). However, insulin has been shown to have detrimental effects on oocyte and embryo competence (Fouladi-Nashta et al. 2005) and to stimulate enzymatic catabolism of progesterone in the liver (Lemley et al. 2008). The latter suggests that glucogenic diets are only of advantage when offered in the immediate postpartum period and are to be avoided when cows are inseminated. In addition, low saturated fat diets around conception, reducing insulin levels, lead to increased conception rates (Garnsworthy et al. 2009).

Soybean meal contains isoflavones in concentrations that are able to induce increases in the blood concentration of estrogenically active isoflavone metabolites (equol, O-desmethylangolensin, dihydrodaidzein) in high-yielding dairy cows postpartum, even when supplemented in relatively low amounts (1.72 kg per day on average) (Cools et al. 2014). When compared with rapeseed meal, soy supplementation was furthermore associated with a decreased angio- and steroidogenesis at the level of the corpus luteum (CL) based on biopsy sampling at day 9 of the estrous cycle. However, no effect on the peripheral progesterone concentration during the first three estrous cycles after calving could be demonstrated. Therefore, although the results of the study suggest negative effects of soy feeding on CL function in recently calved dairy cows, the contribution of this effect on the peripheral progesterone concentration and consequently on overall fertility of supplemented cows warrants further research (Cools et al. 2014).

Adding fats to the diet has been another strategy that has been extensively tested to reduce the impaired reproductive capacity of dairy cows. In a study aiming to minimize the negative energy balance by decreasing the milk fat synthesis, and hence limiting energy output via milk by supplementing the ration with exogenous fats, we were not successful since cows simply produced more milk when reducing the NEBAL (Hostens et al. 2011). Omega-6 fatty acids are believed to have pro-inflammatory, and thus prostaglandin F2α-stimulating, properties rendering them of extra value early postpartum, while omega-3 fatty acids can weaken this inflammatory potency, leading to a higher chance of survival of the embryo when supplemented during the periconception period. However, the consequences of these fat feeding strategies on oocyte and embryo quality remain an intriguing issue for debate. Fat feeding may alter the microenvironment of the growing and maturing oocyte of the early and older embryo and thus may affect reproductive outcome. Dietary-induced hyperlipidemic conditions can thus also be harmful for embryo development and metabolism (for review, see Leroy et al. 2008a, b, c, 2014). Furthermore, peripheral blood in lactating dairy cows will contain a mixture of fatty acids of dietary origin and from body tissue breakdown, the latter being largely abundant in the immediate postpartum period and containing a high proportion of

saturated fatty acids. Especially, the latter have been shown to have a significantly detrimental effect on both the oocyte and embryo quality (Leroy et al. 2005).

Supplementation of extra vitamins and minerals to the diet has often been suggested as the golden bullet solution to reduce the fertility decline. Usually, farmers are highly sensitive to this kind of advice since it does not involve extra labor, which is their paramount constraint nowadays. In herds in which cows are given a high amount of concentrates to sustain peak yield during the immediate postpartum period, the risk of suffering from such deficiencies is lower due to the fact that concentrates are usually highly supplemented with vitamins and minerals. In terms of their effect on immune response and embryo quality, special attention should be given to vitamin E and selenium. The latter was supported by the recent finding that during the dry period, treatment of tocopherol-deficient cattle with injectable vitamin E of 1000 IU each week for the last 3 weeks of gestation not only reduced the incidence of retained placenta and stillbirth but also significantly decreased pregnancy loss (20.5% vs. 12.5%; $P < 0.01$) (Pontes et al. 2015).

3.4 Heat Stress

Embryos are known to be very sensitive to the transient increases in body temperature arising as a result of elevated environmental temperature (heat stress), and dairy cows are very susceptible to heat stress since increasing milk yields interfere with body temperature regulation during warm weather, further exacerbating the deleterious effects on fertility. Heat stress is known to affect many components of the reproductive system including gonadotrophin profiles, follicular growth, granulosa cell function, steroidogenesis, and oocyte and embryo quality (for review see Roth 2008). Interestingly, observations of impaired fertility of dairy cattle in the autumn subsequent to a hot summer have been reported. The latter suggests a clear carry-over effect of heat stress. It seems that heat stress not only affects antral follicles emerging in the follicular wave but probably also affects the ovarian pool of small antral follicles resulting in a carry-over effect on follicular function and oocyte developmental competence.

3.5 Health Problems and Inflammatory Reactions

Forty to seventy percent of dairy cows across different levels of milk production, breeds, and management systems develop metabolic or infectious diseases in the immediate postpartum period (Dobson et al. 2007; Ribeiro et al. 2013). The calving-to-pregnancy interval is extended for at least 7, 8, 26, and 31 days in cows treated for mastitis, retained fetal membranes, hypocalcemia, and endometritis, respectively, compared with healthy herd-mates. Lameness is associated with even worse reproduction performance, as up to 40 days can be lost to get lame cows in-calf

again even though the lameness has been treated (Dobson et al. 2007). In part, these poor fertility data may be related to delayed resumption of ovarian cyclicity after calving and on a lowered expression of heat symptoms. On the other hand, some events seem to have more long-lasting effects. Signs of dystocia or immediate postpartum hypocalcemia, endometritis, or mastitis can be "cured" within days by clinical treatment, but the cows are subfertile many weeks later during the breeding period. Obviously, inflammatory diseases taking place in the first weeks of lactation are associated with a reduced fertilization of cows inseminated between 50 and 60 days postpartum (Santos et al. 2010).

In a recent study, Ribeiro et al. (2016) showed that the carry-over effects of disease on reproduction of dairy cows cannot be explained simply by the nutritional status and its consequences to body condition score and estrous cyclicity at the onset of breeding postpartum. The inflammatory mediators produced by the injured or infected tissues can reach the reproductive tract including ovaries and uterus, but also the brain, which ultimately affects the physiological processes that control normal reproductive cyclicity. For example, cows that suffered from uterine disease postpartum had delayed growth of the first dominant follicle postpartum and reduced concentrations of estradiol (Sheldon et al. 2002). The presence of lipopolysaccharide (LPS; i.e., an endotoxin) in the follicular fluid of cows with uterine diseases has been postulated as a potential reason for compromised steroidogenesis, follicle growth, and impaired oocyte developmental competence (Bromfield et al. 2015).

3.6 Timing of Insults Affecting Reproductive Success and Embryonic Development

More and more evidence is currently indicating that the periconception environment is not only decisive for the fertility of the cow on the short term, but may be as important for general health of the offspring both in the immediate postnatal period and in later life. Specific approaches to improve management of dairy cattle during the periconception period and during pregnancy may therefore not only enhance the reproductive success of the dam but also the growth potential, health, and performance of her offspring later in life. If such innovative approaches could be available for use on the farm, producers might be able to increase animal health concomitantly with an improvement of the quality of the product while reducing costs of production.

The time at which insults are exposed upon dairy cattle will definitely influence reproductive outcome. During the earliest stages of pregnancy, the nutrient requirements of the embryo and young fetus are considered to be very low, causing undernutrition, for example, to be of lesser importance at that stage. Later, in the first trimester, however, development of specific organ systems (e.g., mammary gland, ovaries, liver, and pancreas) takes place. Hence, deleterious insults taking place at that time during pregnancy might be associated with impaired production and

reproductive capacities and a lowered ability to ensure homeostasis in later life. During the second trimester of pregnancy, the fetus continues to develop and grow but, at the end of this stage, will still only reach about 25% of its size at birth. Therefore, and because the dam in most cases won back positive energy balance at that time, the risk of major metabolic challenges is lower during that stage. On the other hand, the development of major organ systems is still going on, so that major insults might still have pronounced effects on later health and productivity. The largest increase in fetal tissue size (75% of fetal growth) generally takes place during the final trimester of pregnancy, insults taking place at that time being mostly reflected in a significantly lowered birth weight.

4 Factors Affecting Periconception Environment in Assisted Reproductive Techniques, Such as Artificial Insemination and Embryo Transfer

4.1 Artificial Insemination (AI)

Artificial insemination (AI) consists of the introduction of sperm into the female genital tract for the purpose of achieving a pregnancy. At present, AI is a mature technique in dairy cattle breeding and established worldwide. Moreover, it yields pregnancy rates similar to natural mating. In a large study comparing AI with natural mating, no difference was found in fertility between both groups (Buckley et al. 2003). Among the adjustment variables in the model, those significantly associated with the likelihood of conception rate to first service included the herd, calving period, calving to first-service interval, and peak milk yield (as discussed above).

In general, frozen semen is used for AI in cattle; semen samples are thawed just before use and are deposited into the corpus uteri. Sperm numbers introduced vary around ten million live sperm cells (20 million frozen per straw), but it has been shown that numbers as low as two million give equally good pregnancy rates (49–53%) and that deep insemination into the uterine horn is not necessary (Verberckmoes et al. 2005). Deep insemination with normal dose of semen did not improve fertilization rates or embryo production in superovulated cattle (Carvalho et al. 2013). In one study in beef cattle, however, deep insemination gave better results (67% vs 49%) with low-dose (four million) semen than conventional insemination (Meirelles et al. 2012). Deep insemination of frozen-thawed semen into the uterine horns gives also better results in pigs (Vazquez et al. 2008), and in sheep, laparoscopic insemination with frozen-thawed semen deposition into the uterine horns has been the routine procedure for many decades, since vaginal or even deep cervical insemination is yielding much lower results (Evans 1988).

Detection of estrus is very important when performing AI, and results can easily be influenced by this aspect. In order to make the timing of artificial insemination (AI) relative to ovulation less critical, methods for prolonging shelf life of

spermatozoa in vivo after AI have been developed. Encapsulation of sperm cells is a documented technology, and recently, a technology in which sperm cells are embedded in alginate gel has been introduced and commercialized. A blind field trial has been performed in Norway using standard processed semen with the Biladyl extender (control) in comparison with semen processed by sperm immobilization technology developed by SpermVital AS (Standerholen et al. 2015). Here it was demonstrated that fertility was not affected by encapsulation (NRR in both groups of 73%), although higher percentages of acrosome-damaged sperm were present in the encapsulated group. This shows that AI is a mature technique and can be used with different types of semen.

However, differences in bull fertility remain a problem. Nowadays, differences between bulls in field fertility have been related to the presence of "compensable" and "uncompensable" effects (Saacke 2008). Males requiring more sperm to be fertile after AI are considered to have compensable seminal deficiencies. This was elegantly shown by Den Daas et al. (1998), in a field trial where it became clear that the minimum sperm numbers required to achieve maximum pregnancy rates differ between bulls. These so-called compensable seminal deficiencies include a number of known sperm viability and morphology traits preventing fertilization to occur at all. Differences in fertility among males independent of sperm dosage are considered "uncompensable." These seminal deficiencies are associated with fertilizing sperms that are incompetent to maintain the fertilization process or subsequent embryogenesis (once initiated), leading to early embryonic mortality (Saacke 2008). It is obvious that compensable differences between males are more important in the AI industry than in extensive breeding systems, since AI with low doses of semen is economically more profitable, and hence bulls with compensable traits, which do not perform well at low doses, are less attractive and therefore are in less demand. Also interesting though are the uncompensable traits: can they be induced by environmental influences, with stressors having deleterious effects upon spermatogonia of the young or even prepubertal bull, or even earlier, when a male fetus was being exposed in utero to an adverse periconception environment? This may seem farfetched and has not been investigated in cattle yet, but in mice there have been several studies that show an effect of in utero exposure on future male fertility of offspring, even for several generations. In some recent animal studies, mostly in mice and rats, transgenerational inheritance of acquired traits has been demonstrated. One such study examined the effect of endocrine disruptors on pregnant rats and their offspring (Anway et al. 2005). To this end, rats were injected with vinclozolin (an antiandrogenic endocrine disruptor) at 8–15 days post-coitum, which is the period of gonadal sex determination. Transient exposure of a gestating female rat to endocrine disruptors induced an adult phenotype in the F1 generation of increased incidence of male infertility. These effects were transferred through the male germ line to nearly all males of all subsequent generations examined (i.e., F1 to F4) (Anway et al. 2005). The effects on reproduction correlate with altered DNA methylation patterns in the germ line (Anway and Skinner 2008). However, when a similar study was performed by orally exposing pregnant rats to vinclozolin, to test

a more natural route, no effect on male fertility in F1 or subsequent generations was found (Schneider et al. 2008).

Similar data are more difficult to achieve in large animal models, because of the large generation interval. Most large animal studies focus on the F1 generation to evaluate an effect of the environment on the offspring – it is important that such studies are also being performed on bulls and other large male mammals.

At present, there is no indication that calves produced after AI are less viable or less fertile than calves produced after natural mating, but this has apparently not been investigated yet (no hits on PubMed with calves * natural mating * insemination). It has been argued however that sex ratio may be skewed after artificial insemination, leading to more male calves (Berry and Cromie 2007). This was not confirmed in another study performed in Ethiopia, where a normal sex ratio of 50:50 was found after AI, but with odds ratio 1.38 for female calves after natural mating (Delesa et al. 2014). This was probably due to the fact that cattle that came into estrus during the harsh season were more likely to give birth to a female calf, according to the Trivers and Willard hypothesis (Trivers and Willard 1973) which states that as maternal condition declines, the adult female tends to produce a lower ratio of males to females.

However, the perception that AI gives more males than natural mating, which was obvious from both studies, needs further investigation, since such assumptions may prevent AI from being introduced at a large scale in Africa, where female cattle are much preferred over male calves.

4.2 Multiple Ovulation and Embryo Transfer (MOET)

Multiple ovulation and embryo transfer has been used in farm animals since the early 1980s (Thibier 2005). It consists of the use of multiple hormone injections to induce the release of multiple oocytes from the ovaries (so-called superovulation), followed by AI, flushing of the embryos from the uterus and transfer of the resulting embryos into synchronized recipients. Therefore, this technique increased offspring from genetically valuable females, while reducing also the time between generations. The major disadvantage of MOET is the unpredictable response of the donor female to exogenous superovulation treatment: 20% do not react sufficiently, whereas in *Bos taurus* an average of five to six embryos can be expected.

Multiple ovulation or superovulation has been reported to induce changes in gene expression and DNA methylation patterns in several species. In addition, the use of high dosages of gonadotropins induced spindle and chromosomal abnormalities in bovine oocytes (Liu et al. 2011). In mice, *H19*, *Snrpn*, *Peg3*, and *Peg1* showed loss of DNA methylation in mouse blastocysts obtained after superovulation, and this alteration was dose dependent, with aberrant methylation more frequent at high hormone dosage (Market-Velker et al. 2010b). Importantly, the loss of DNA methylation of *H19*, *Snrpn*, and *Peg1* could be observed in the sperm of the mouse off-

spring during two generations (Stouder et al. 2009). Superovulation in mice also resulted in biallelic expression of *Snrpn* and *H19* imprinted genes in the placenta (Fortier et al. 2008).

4.3 In Vitro Embryo Production (IVP)

In vitro embryo production entails the combination of three steps that need to be performed following a strict timing. It covers all steps from the maturation and fertilization of the oocyte to the embryo development. The oocytes can be derived both from a living (by transvaginal ovum pickup) or dead animal (slaughterhouse-derived ovaries). It is also combined with embryo transfer in many species.

4.3.1 In Vitro Embryo Production Affects Embryo Development and Quality

Cleavage and blastocyst rates are the main noninvasive parameters to assess bovine embryo quality. However, over time, it has become evident that high cleavage/blastocyst rates do not necessarily correlate with excellent quality of IVP embryos. Therefore, other criteria have been introduced, to compare with in vivo-derived cattle embryos. It is clear that IVP embryos show a darker cytoplasm due to their higher lipid content (Pollard and Leibo 1994), a more fragile zona pellucida (Duby et al. 1997), differences in metabolism (Khurana and Niemann 2000), a reduced intracellular communication (Boni et al. 1999), higher incidence of chromosome abnormalities (Viuff et al. 1996; Lonergan et al. 2004), errors of imprinting (Doherty et al. 2000), slower growth rate, higher thermal sensitivity, lower ICM/TE cell ratio (Van Soom et al. 1997a, b), and differences in gene expression compared to their in vivo counterparts (Driver et al. 2012). Additionally, higher apoptotic rates have been reported in IVP embryos compared to their in vivo counterparts (Gjørret et al. 2003), with an increased incidence of apoptosis as the culture time increases (Vandaele et al. 2006). Surprisingly, in cattle, some media used for in vitro culture are reported to have an influence on the sex ratio of the produced embryos, with a shift toward male embryos (Massip et al. 1996; Gutierrez-Adan et al. 2001).

4.3.2 Effects of In Vitro Embryo Production on Gene Expression

Gene expression is definitely different in IVP embryos. Before the development of wide screening techniques (such as microarray and RNA-seq), the effort was focused on genes known to play important roles during pre- and postimplantation development. The expression of *DNMT1*, *3A*, and *3B* has been demonstrated to be upregulated in bovine oocytes after in vitro maturation (IVM) compared to

in vivo-matured oocytes (Heinzmann et al. 2011). In vitro embryo culture was shown to have a major effect on gene expression, which is logical since embryos spend 7–8 days in that environment. A microarray study showed that approximately 85% of differentially expressed genes was downregulated in IVP bovine blastocysts compared to their in vivo counterparts (Corcoran et al. 2006). Most of these genes are involved in transcriptional and translational events suggesting that a deficient machinery associated with transcription and translation is behind the inferior quality of IVP embryos (Corcoran et al. 2006). Furthermore, different culture media had a different impact on genes associated with transcription and translation (Corcoran et al. 2007). This is not a unique case; genes involved in blastocyst formation such as cell-to-cell adhesion (E-cadherin, connexins, TJ genes), cell communication (gap junctions), differentiation marks (Miller et al. 2003; Lonergan et al. 2003a, b; Boni et al. 1999), and genes related to apoptosis and oxidative stress (*BAX*, *SOX*, *HSP70*) had different expression patterns between different culture media (Sagirkaya et al. 2006; Rizos et al. 2002).

When comparing in vivo-derived IVP bovine embryos, genes related to metabolism, growth, and differentiation (*GLUT-5*, *CX43*, *IGF-II*, *LIF*) were upregulated in embryos derived in vivo, while genes related to stress (*SOX*, *MnSOD*, *BAX*, *HSP70.1*, *PRDX5*) were upregulated in IVP embryos. The significant increase in expression of those genes supports the hypothesis that current in vitro culture systems are associated with a considerable amount of oxidative stress (Rizos et al. 2003; Lazzari et al. 2002). Additionally, in embryos produced in vitro in the absence of fetal bovine serum (FBS), the expression of genes involved in the cholesterol biosynthesis pathway was upregulated compared to in vivo-derived embryos (Driver et al. 2012). In addition to culture media composition, culture conditions such as oxygen concentrations were shown to have an impact on gene expression (Harvey et al. 2004).

Other ARTs also induce alterations on the transcriptome. Some studies reported differences in the mRNA expression profile of several genes between embryos produced with sex-sorted and unsorted semen (Morton et al. 2007), while other studies failed to find differences (Bermejo-Alvarez et al. 2010). Nevertheless, offspring from sex-sorted spermatozoa did not display more abnormalities than the controls (Seidel and Garner 2002). Vitrification of mouse oocytes arrested at MII induced downregulation of *Dnmt1*, *1o*, *3A*, *3B*, and *3 L* in MII and of *Dnmt3B* in blastocysts (reviewed by Anckaert and Fair 2015). Furthermore, blastocyst vitrification altered the microRNA transcriptome of mouse embryos. Four miRNAs (mmu-miR-199a-5p, mmu-miR-329-3p, mmu-miR-136-5p, and mmu-miR-16-1-3p) were upregulated, and one (mmu-miR-212-3p) was downregulated in vitrified compared to fresh mouse blastocysts (Zhao et al. 2015). Additionally, superovulation induced alterations in the gene expression of bovine oocytes (Chu et al. 2012). Despite all this, a similar expression of developmentally important genes was observed between in vivo and IVP embryos carried to term (Ghanem et al. 2011).

4.3.3 Effects of ARTs on Epigenetic Marks

The study of the effects of ARTs on the epigenetic pattern of the embryos and resulting offspring has gained more attention in recent years. IVP increased the levels of DNA methylation compared to embryos derived in vivo, in rats and mice (Zaitseva et al. 2007). In bovine blastocysts, IVP altered the DNA methylation profile, with longer in vitro culture being translated in higher alteration compared to in vivo-derived embryos (Salilew-Wondim et al. 2015). Cloned embryos also showed aberrant DNA methylation patterns in several species, including cattle (Dean et al. 2003) and sheep (Beaujean et al. 2004). However, in rabbits no differences in DNA methylation status were observed between cloned and IVP embryos (Shi et al. 2004).

Alterations of imprinting have been observed in embryos, placenta, and offspring produced by ARTs. A loss of DNA methylation in *Igf2R* and *Peg1* and a gain of methylation in *H19* were found after IVM compared to in vivo maturation in mice. This gain of methylation in *H19* was also reported in humans after IVM in five out of 20 oocytes analyzed (reviewed by Ventura-Juncá et al. 2015).

In the mouse, loss of DNA methylation was reported in *H19*, *Snrpn*, and *Peg3* in IVP embryos using different culture media (Market-Velker et al. 2010a; Doherty et al. 2000). Additionally, serum supplementation induced alterations on the DNA methylation pattern of various imprinted genes (*H19*, *Igf2*, *Grb7*, *Grb10*, and *Peg1*), faster rates of development, and long-term behavioral consequences in mouse embryos (reviewed by Velker et al. 2012a). Vitrification also altered the methylation status of imprinted genes, causing a loss of methylation in *H19* in murine embryos (Wang et al. 2010).

A condition of overgrowth can be induced by ART in ruminants and is referred to as large offspring syndrome (LOS). It is characterized by large size at birth, breathing difficulties, reluctance to suckle, and sudden perinatal death (Young et al. 1998). LOS is caused by the exposure of pre-elongation ruminant embryos to unusual environmental conditions. It is not exactly clear what environmental changes are important, but a major cause is the use of serum in the culture media (Sinclair et al. 1999). Recent studies provide evidence for epigenetic changes in LOS as this syndrome shows dysregulation of several similar imprinted genes such as *IGF2R*, *KCNQ1OT1*, or *CDKN1C* (Chen et al. 2013, 2015). Furthermore, loss of maternal-specific *SNRPN* methylation was found in the placentae from in vitro-fertilized and in vitro-cultured bovine embryos (reviewed by Velker et al. 2012b). We have recently used RNA sequencing to examine the effect of in vitro embryo production, in either serum-containing or serum-free media, on the global gene expression pattern of individual bovine blastocysts. Compared to in vivo-derived embryos, embryos produced in serum-containing medium had five times more differentially expressed genes than embryos produced in serum-free conditions (1109 vs. 207). Importantly, in vitro production in the presence of serum appeared to have a different impact on the embryos according to their sex, with male embryos having three times more genes differentially expressed than their female counterparts (1283 vs. 456). On the contrary, male and female embryos produced in serum-free conditions showed the same number (191 vs. 192) of genes expressed differentially;

however, only 44 of those genes were common in both comparisons. Interestingly, the pathways affected by in vitro production differed depending on the presence or absence of serum in the medium. For example, embryos produced in serum-containing conditions had a lower expression of genes related to metabolism, while embryos produced in serum-free conditions showed aberrations in genes involved in lipid metabolism (Heras et al. 2016).

5 Conclusion

In conclusion, the periconception environment plays an important role in natural and assisted breeding of cattle. Changes in nutrition, temperature, metabolic status, or health status during natural breeding can affect reproductive success and offspring health. Likewise, changes in medium composition or the presence of stressors to which gametes or embryos are exposed can also influence reproductive success and offspring health in assisted reproduction. Recent research in herd health management and follow-up on offspring will help us to improve management of high-producing dairy cattle, and recent advances of "omics" technologies may enable the application of new molecular methods for the identification of signaling molecules which are imposing epigenetic marks upon gametes and embryos during early life, thereby affecting also reproductive success and offspring health.

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