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Impact of maternal malnutrition during the periconceptional period on mammalian preimplantation embryo development

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ABSTRACT

During episodes of undernutrition and overnutrition the mammalian preimplantation embryo undergoes molecular and metabolic adaptations to cope with nutrient deficits or excesses. Maternal adaptations also take place to keep a nutritional microenvironment favorable for oocyte development and embryo formation. This maternal-embryo communication takes place via several nutritional mediators. Although adaptive responses to malnutrition by both the mother and the embryo may ensure blastocyst formation, the resultant quality of the embryo can be compromised, leading to early pregnancy failure. Still, studies have shown that, although early embryonic mortality can be induced during malnutrition, the preimplantation embryo possesses an enormous plasticity that allows it to implant and achieve a full-term pregnancy under nutritional stress, even in extreme cases of malnutrition. This developmental strategy, however, may come with a price, as shown by the adverse developmental programming induced by even subtle nutritional challenges exerted exclusively during folliculogenesis and the preimplantation period, resulting in offspring with a higher risk of developing deleterious phenotypes in adulthood. Overall, current evidence indicates that malnutrition during the periconceptional period can induce cellular and molecular alterations in preimplantation embryos with repercussions for fertility and postnatal health.

1. Introduction

The preimplantation embryo is a pivotal developmental stage in mammalian species. During the preimplantation period cellular and molecular milestones take place, including genome activation, the formation of adhesive cell contacts, and the establishment of founder cell lineages at the blastocyst stage [1]. Great part of its development critically depends on the nutritional microenvironment present in ovaries and reproductive tract. Cattle have proved to be a suitable animal model for embryonic research and have been used extensively to develop experimental studies on nutrition and reproduction. Accordingly, nutrition has been identified as one of the most important factors affecting fertility in cattle [2]. The most common bovine model for in vivo preimplantation embryo research is superovulated cattle. Early experiments studying the effects of nutrition on in vivo embryo production with exogenous gonadotrophins were carried out when knowledge on bovine superovulatory physiology was scarce, limiting the reliability of data [3–5]. Nowadays, bovine superovulatory programs are relatively well-established procedures [6,7], and evidence has shown that the nutritional plane of embryo donors plays a critical role in the outcome of bovine superovulation [8,9]. A low plane of nutrition (ie, below their maintenance nutritional requirements) can impact negatively the superovulatory response in beef heifers [10]. Likewise, in superovulated

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high-yielding dairy cows, a low body condition score (BCS) can compromise the number of embryos with good morphological quality [11]. However, there is evidence indicating that overnutrition can also impair embryo production in both beef [12] and dairy cattle [13,14]. Therefore, proper nutritional balancing is critical for the development of good quality embryos. This review addresses the link between overall nutritional status of macronutrients during the periconceptional period (ie, from folliculogenesis to early embryo development before implantation) and preimplantation embryo development with emphasis in ruminant species. Information from other mammalian species is also discussed with the aim of providing possible physiological pathways mediating the effects of malnutrition (ie, undernutrition and overnutrition) on mammalian preimplantation embryo development.

2. Overnutrition and undernutrition may impair preimplantation embryo development

2.1. Undernutrition

Undernutrition may originate from a deficient bioavailability of one or more macronutrients and micronutrients. This nutrient deficiency can be caused by decreased dietary intake, increased nutritional losses, or impaired ability to utilize nutrients [15]. Current cattle production systems provide dietary regimens aimed at maintaining a positive energy balance to exploit the full genetic potential of cattle herds. Still, occurrence of negative energy balance (NEB) during the early postpartum period has been characterized, especially in high-yielding dairy cows [16]. This period of NEB is partially associated with a lack of dietary intake capacity to meet the increasing energy demands for high milk yield imposed by genetic selection [17]. In conditions where nutrient availability is not an issue (ie, animals have access to diets that can cover their nutritional requirements for lactation), NEB in beef cows is virtually absent or less severe [18,19]. This seems to be partially associated with an attenuated growth hormone/insulin-like growth factor (GH/IGF) axis responsiveness [19–21] and a lower number of secretary cells and activity per cell in the udder [22]. High-yielding dairy cows in NEB during lactation usually display a poor BCS associated with an impaired metabolic status, including high levels of nonesterified fatty acids (NEFA) and β-hydroxybutyrate, and low concentrations of insulin, insulin-like growth factor-1 (IGF-1), glucose, and leptin [23–25].

The impaired metabolic status during NEB may reduce oocyte quality as demonstrated by Leroy et al [26] who found that oocytes exposed in vitro to NEFA concentrations found in ovarian follicular fluid of dairy cows in NEB displayed an increased apoptosis of cumulus cells and impaired progression of meiosis with subsequent negative effects on cleavage rate and blastocyst formation. Using a similar model, it was reported that in vitro oocyte maturation in a high β-hydroxybutyrate microenvironment resulted in reduced cleavage rate and blastocyst yield, but only in combination with low concentrations of glucose [27]. Moreover, recent data suggested that the oviductal-uterine microenvironment in early postpartum dairy cows has a reduced capability to support normal early embryo development compared with nulliparous dairy heifers [28] and nonlactating dairy cows [29], which might be partially related to an impaired IGF bioavailability in oviducts during NEB [30,31]. Indeed, superovulated elite dairy donor cows with good BCS (2.5–3.5 in a scale from 1 to 5) produced more viable embryos than cows in poor BCS (BCS <2.5 in a scale from 1 to 5, Fig. 1A), and the increase in embryo production was linked to a better metabolic status associated with increased circulating concentrations of insulin and IGF-1 [11] (Fig. 1B). Supplementation of in vitro culture medium with these hormones has been associated with a higher rate of blastocyst formation and an increased number of cells and reduced occurrence of apoptosis at the blastocyst stage [32].

However, blastocyst formation may not always be compromised by undernutrition, as shown recently with an ovum pick-up/in vitro fertilization (OPU/IVF) model in lactating dairy cows in which embryo production was not different between two postpartum periods presenting significant differences in blood analytes of reproductive relevance [33]. These results could be partially attributed to the fact that blood concentrations of hormones and metabolites capable of affecting oocyte physiology do not always reflect ovarian intrafollicular concentrations accurately, especially in cattle undergoing nutrition-related metabolic challenges [34–36]. In a recent study in humans, ovarian follicular fluid concentrations of cholesterol, NEFA, glucose, insulin, and IGF-1 were lower than in serum even though a significant correlation between serum and follicular fluid concentrations was present in most of the analytes measured [37]. In cattle and sheep, it has been reported that different BCS, level of feed intake, or fasting, although significantly affecting IGF-1 concentrations in blood, did not alter levels in ovarian follicular fluid [34,38]. This is believed to represent a mechanism aimed at protecting the oocyte in the developing follicle from deficits and/or deleterious rises in circulating blood analytes during malnutrition [26]. The relationship between these body fluid compartments is even more complex when considering that concentrations of follicular fluid analytes can be affected by the size [39,40] and estrogenic status of ovarian follicles [41,42], which is challenging to monitor in OPU/IVF cycles. It also has to be taken into account that some cows can preserve their fertility under nutritional stress [43] and that sublethal application of several stressors such as high hydrostatic pressure, or osmotic, heat, and oxidative stress can increase fertilizing ability and developmental potential of embryos [44,45]. Even women with serious eating disorders (eg, anorexia nervosa and bulimia nervosa) can achieve pregnancy and delivery to term [46,47]. Evidence suggests that this might be related to adaptations of paracrine pathways important for female fertility, such as the IGF axis. For instance, it is known that dairy/beef crossbred cows with low BCS during the postpartum period can increase protein expression of the IGF-1 receptor (IGF-1R) in the ovary [48] and that rats subjected to undernutrition can upregulate IGF-1R messenger RNA (mRNA) expression in the hypothalamus [49]. Similarly, sheep undergoing short-term food restriction with 0.5 of their maintenance nutritional requirements (M) increased their ovarian intrafollicular insulin levels over those found in control counterparts fed with 1 M, resulting in no significant