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Impact of nutritional stress on early embryonic survival

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ABSTRACT

Low reproductive efficiency is the utmost critical predicament faced by the modern livestock industry across the globe. Early embryonic loss is one of the major causes of poor reproductive efficiency resulting in delayed pregnancy, fewer calves born, reduced milk production, slower genetic progression, and substantial financial loss to the beef and/or dairy industry. The establishment of pregnancy results from the interaction between the embryo and the dam and is the culmination of a series of events initiated with development of the follicle and gametes. Among numerous internal and external factors, nutrition has the potential to alter the microenvironment of the oocyte and the embryo, making it more hostile to optimal fertilization and pre-implantation embryonic growth. Understanding the impact of nutritional stress on oocyte function, embryo development and reciprocal signaling networks between the embryo and uterus will lead to alleviation of the problems associated with early embryonic mortality.

Keywords: Early embryonic loss, establishment of pregnancy, maternal recognition of pregnancy, interferon-tau, progesterone, nutritional stress, oocyte function, embryo development

INTRODUCTION

Early embryonic mortality is a major cause of reproductive failure during the preimplantation period, which is when the embryo and uterus develop in a coordinated synchronous manner. Early embryonic loss during this critical period may be due to embryo-uterine asynchrony (1), early increase in endometrial PGF2alpha ($PGF_{2\alpha}$) secretion (2), and delay in or insufficient production of interferon-tau (IFNτ) by the conceptus (3), resulting in delay or failure to signal its presence to the mother for maternal recognition of pregnancy (MRP) and heat stress. It significantly limits the success of establishment and maintenance of pregnancy in ruminants and it is a major impediment for the adoption of a range of assisted reproductive technology in the

breeding industry. The higher proportion of embryo loss occurs in the first 8-19 days after artificial insemination (AI) when the early embryo is completely dependent on the oviduct and uterine environment for its survival (4). The establishment of pregnancy results from the interaction between the embryo and the dam and is the culmination of a series of events initiated with development of the follicle and gametes. It involves maternal recognition of pregnancy and implantation. MRP is the physiological process whereby the conceptus signals its presence to the mother and prolongs the lifespan of the corpus luteum (CL) in order to maintain progesterone (P_4) production (5). The ruminant conceptus secretes the pregnancy recognition signal, interferon tau (IFNτ), which prevents luteolysis of the CL. The CL produces progesterone (P_4), which is required for the initiation and maintenance of pregnancy by making the uterus a permissive environment for conceptus development, implantation, placentation and successful fetal and placental development to term (6). Understanding the root causes of pre-implantation and post-implantation fetal losses is required to design strategies towards improving the efficiency of in vitro fertilization and pre-implantation genetic diagnosis. Of the various environmental factors known to affect oocyte and embryo development, altered nutrition prior to conception and during the early stages of pregnancy is one of the major intriguing factors involved in early embryonic loss. Nutrition plays a notorious role in determining the success of the embryo in establishment and maintenance of pregnancy. Nutritional stress has been found to enhance embryonic wastages by altering follicular development, oocyte quality, embryo quality, uterine gene expression, and embryo-mother signaling (7). This review will highlight maternal recognition of pregnancy and impact of nutritional stress on developing oocyte, early embryo and endometrium during maternal recognition of pregnancy events that will facilitate the development of strategies to augment early embryo survival.

Regulation of luteolysis

The estrous cycle consists of a series of predictable physiological events that occur between successive periods of sexual receptivity, also known as estrus. These series of reproductive events occur throughout the female's adult life until it is interrupted by pregnancy and, in some species, season of the year. The estrous cycle can be divided into four stages viz., estrus, metestrus and diestrus, proestrus. Estrus is the sexually receptive phase and begins with the acceptance of the male and lasts for 18 hr varying within a range of 18 to 24 hr (8). During estrus, the estrogen and FSH are declining accompanied by LH surges during standing estrus. During this time, the theca cells start producing progesterone to inhibit LH and FSH release and ovulation occurs 12-18 hrs after the end of estrus. Estrus phase is followed by metestrus, which lasts for 5 or 7 days and occurs on 1-5 days of the cycle. Ovulation occurs within the metestrus phase that is 24-30 hr after the onset of estrus. During this phase, the FSH surge that occurs during this time may recruit the first follicular wave for the next cycle. Diestrus is the lengthiest phase and occurs on 6-17 days of the cycle. During this time the CL will be functional and produces increasing levels of P4. If pregnancy occurs, the CL will be maintained throughout the pregnancy period, if not the CL will be maintained until 17 or 18 days of the cycle and regresses thereafter (9). Proestrus occurs on 19-21 days of the cycle and lasts for 3 days; it starts with regression of CL and reduction in progesterone (P_4) levels (8) with concurrent follicular growth and estradiol (E_2) production by the ovary (9). The physiological and hormonal changes that

occur during the estrous cycle prepare the reproductive tract of the female animal for the period of sexual receptivity, ovulation and implantation. Therefore, understanding the biological mechanisms, the physiology, hormonal regulation, and molecular events of the estrous cycle is essential for increasing the pregnancy rates of farm animals.

In ruminants, the oestrus cycle is dependent on the uterus as the pulsatile secretion of prostaglandin F2α ($PGF_{2\alpha}$) from the endometrium results in functional and structural regression of the ovarian CL, termed luteolysis. $PGF_{2\alpha}$ is transferred locally to the ovary by a countercurrent mechanism and acts on the CL causing its destruction and a decline in P_4 secretion (10). Two main phases of luteolysis include: 1) a loss of ability to synthesize and secrete progesterone and 2) the structural demise of the CL itself (11). During the early luteal phase, progesterone acts through endometrial progesterone receptors (PR) to inhibit estrogen receptor (ER) and oxytocin receptor (OTR) expression in endometrium for 10-12 days. This period is termed as progesterone block period. However, progesterone gradually down regulates PR expression in endometrial epithelium and loses its ability to suppress endometrial estrogen receptor and oxytocin receptor expression. Estrogen then increases the formation of estrogen and oxytocin receptors. Thus, increase in abundance of estrogen and estrogen receptors promote both oxytocin receptor formation and a change in the pattern of $PGF_{2\propto}$ release, which results in luteolysis. During pregnancy recognition period, the conceptus extends the progesterone block to ER and OTR to prevent the pulsatile pattern of luteolytic $PGF_{2\propto}$. Endometrial ER and PR are highest during the first 10-12 days after onset of estrus in cows and then both decline to their lowest levels on about Day 13. ER then increases between days 14 and 15, with OTR increasing rapidly between days 17 and 21. In sheep and goats, endometrial oxytocin receptors increase rapidly 48-72 hr prior to estrus (12, 13). Low endometrial PR, increasing endometrial ER and OTR characterize the luteolytic period. In cyclic ewes endometrial PR and PR mRNA decrease from Days 10-14 and then increase on Day 16 after luteolysis. OTR mRNA and protein increase between day 14 and estrus. This coincides with increasing ER, ER mRNA, OTR and OTR mRNA between day 14 and estrus.

$PGF_{2\alpha}$ is considered a luteolysin and causes luteolysis by abating progesterone production and inducing the structural demise of the CL, mediated by the endothelial cell derived vasoconstrictive peptide known as endothelin-1 (ET-1) (14). $PGF_{2\alpha}$ is thought to activate the ET-1 gene in luteal endothelial cells, thus stimulating ET-1 production. ET-1 secretion then further stimulates luteal $PGF_{2\alpha}$ production, which will act in a paracrine manner on the CL to further enhance ET-1 synthesis and secretion (10, 15). ET-1 binds to a specific receptors found on both small and large luteal cells. This activation then decreases both basal and LH-induced production of progesterone, possibly by interrupting the cAMP mediated pathway leading to progesterone production (14) in rats (16) and pigs (17). At the time of structural luteolysis in cow and ewe, it was shown that both ET-1 concentration and mRNA encoding for ET-1 were greatest in luteal tissue at this time (14). Further evidence shows that ET-1 blocks progesterone production in bovine and ovine luteal cell culture and $PGF_{2\alpha}$ treatment stimulates ET-1 expression and secretion in these luteal cells (18, 19). Several groups have shown that $PGF_{2\alpha}$ elevates TNF-α production by macrophages in both the bovine and ovine CL (20, 21). There is evidence to suggest that TNFα induced apoptosis plays a role in structural luteolysis. Several reports indicate that apoptosis occurs during luteolysis in ruminants (22, 23, 24), while there is a strong

correlation between apoptosis and maximal expression for $PGF_{2\alpha}$ receptor mRNA in rodents (25). $PGF_{2\alpha}$ elevates TNFα levels in both the bovine and ovine CL and demonstrated that endothelial cells express high levels of TNFRI, a TNFα receptor type, and that they are sensitive to TNFα-induced apoptosis *in vitro* (20). ET-1 has been found to play a key role in functional luteolysis through the inhibition of progesterone production by luteal cells and TNFα has been linked to apoptosis in luteal endothelial cells. It has previously been hypothesized that during early and mid-luteal phases the high levels of progesterone that still persist in conjunction with the low levels of TNFα and a TNFR1 prevent apoptosis in endothelial cells. It seems the progesterone producing cells are resistant to apoptosis and serves to protect the luteal cells (26). However, at the time of luteolysis, $PGF_{2\alpha}$ stimulates ET-1 secretion by luteal cells and TNFα production by local macrophages up-regulation of one another's production via a positive feedback loop, which synergize to inhibit progesterone production. These low progesterone levels in conjunction with increased TNFR1 expression (20, 21) facilitate TNFα apoptosis of the endothelial cells in the CL leading to functional and structural luteolysis (26).

Maternal recognition of pregnancy

Maternal recognition of pregnancy in livestock involves independent interaction between conceptus and uterus as well as between conceptus and the ovary. It is defined as the uterine recognition of conceptus (es) signal and extension of the ovarian corpus luteum (CL) life span, which occur in a coordinated synchronous manner if pregnancy is established. This recognition is critical so that the endometrium does not secrete prostaglandin$F_{2\alpha}$ ($PGF_{2\alpha}$), which will lyse the CL and destroy the source of progesterone, the hormone necessary to sustain a pregnancy. There are two categories of the mechanism of maternal recognition: luteotrophic or anti-luteolytic. Luteotrophic directly promotes luteal function, supporting the CL, and anti-luteolytic prevents the uterine release of luteolytic $PGF_{2\alpha}$, which causes the lysis of the CL. Cattle, sheep, pigs, mice, and humans/non- human primates are among the most well studied species regarding maternal recognition of pregnancy.

Humans/non-human primates and rodents maintain luteal function through luteotrophic mechanisms. In primates the maternal recognition signal is chorionic gonadotropin (CG) (27). The syncytiotrophoblast cells secrete CG from days 8-10 post-ovulation for pregnancy recognition. At the same time, days 7-9, implantation is occurring. CG stimulates the CL to produce progesterone until there is a shift between luteal and placental progesterone secretion. Once the shift occurs, CG secretion decreases. Administration of exogenous CG can also extend the luteal function of the CL and increase progesterone secretion in humans and non-human primates (28). Rodents also maintain luteal function through luteotrophic mechanisms, using prolactin as the maternal recognition of pregnancy signal (29). Prolactin, from the anterior pituitary gland, is induced by mating (30). It is the initial maternal recognition signal until day 12 of pregnancy. After day 12, the conceptus and uterine decidua take over the stimulating progesterone secretion by secreting lactogenic hormones (prolactins). These hormones act on the luteal cells through the prolactin receptors to maintain luteal cell function and the secretion of progesterone (30). The other mechanism for maternal recognition of pregnancy is an anti-luteolytic mechanism. The MRP signal for cattle and sheep is interferon-tau (IFNτ) (31). Maternal recognition of pregnancy in cattle and sheep was first investigated in the 1960s, by

Moor and Rowson, who determined that the presence of a viable embryo by day 12 and 16 post-estrus in ewes and cows, respectively, was required for the continuation of CL function beyond the time of a normal estrous cycle (32, 33). The nature of this factor remained unknown until Martal et al. (34) discovered the embryo-derived factor, initially termed trophoblastin, was proteinaceous in nature. It is secreted in large quantities by the mononucleate cells of the trophectoderm as the blastocyst begins to elongate at approximately day 13 in cattle at a peak production when the conceptus reaches its maximal size (35). IFNτ mRNA is expressed for a brief period of time during maternal recognition, beginning early in bovine embryo development and reaching peak gene expression at day 14 coincident with the onset of conceptus elongation in cattle (36, 37). IFNτ mRNA can be detected until approximately day 25 of development but is not expressed thereafter (36). IFNτ protein can be detected in conditioned medium as early as the late morula or the early blastocyst stage of development, approximately day 6-7 post-fertilization (38). Although IFNτ mRNA abundance reaches its peak at day 13-14 of development, the overall production of IFNτ protein continues to increase between days 13 and 19 of pregnancy due to the considerable growth of trophectoderm over this period of development (39). In sheep, IFNτ is secreted between days 10-21 by the mononuclear trophoblast cells (31). On days 11-16, the $PGF_{2\alpha}$ concentrations are the same in pregnant and non-pregnant animals, but pregnant animals that administered $PGF_{2\alpha}$ on day 19 or 20 do not return to estrus (28). In *vitro* culture of sheep, conceptus homogenates and analysis for radiolabelled proteins released into the culture medium indicates mononuclear cells of ovine trophoectoectoderm secrete oTP-1. oTP-1 is secreted in two phases: once between days 10 and 21 of pregnancy and then by chorion between days 25 and 45 of pregnancy. oTP-1 is thought to exert a paracrine antiluteolytic effect on the endometrium as there is no evidence that it is transported from uterus to directly affect CL. Secretion of oTP-1 (ng/uterine flushing) begins on about day 10 and increases with the morphological changes : from spherical (312 ng) to tubular (1380 ng) to filamentous (4455 ng) forms on days 12-13. Intrauterine injections of homogenates from days 14-16 allowed ovine embryos to successfully maintain the CL lifespan by one month, while intrauterine injections of homogenates from days 21-23 showed ovine embryos did not have extended CL lifespans (40). Goat conceptus secretes caprine IFNτ between days 16-21 that is assumed to be antiluteolytic signal. IFNτ acts in the same manner in cattle as it does in sheep, by suppressing the transcription of estrogen receptor, therefore decreasing estrogen induced oxytocin receptor, decreasing the $PGF_{2\alpha}$ cascade. Ovarian follicular development is suppressed in the ovary with the CL, but not the contralateral CL. This also results in decreased levels of estrogen. Pigs also have an anti-luteolytic mechanism of maternal recognition of pregnancy and this signal is estrogen (41). Estrogen is produced by the conceptus on days 11 and 12. Estrogen does not cause a decrease in $PGF_{2\alpha}$ secretion from the endometrium, but instead redirects PGF secretion from the uterine vasculature to the uterine lumen. The $PGF_{2\alpha}$ is sequestered and metabolized in the uterine lumen to prevent it from reaching the CL and initiating luteolysis (41). There is also a shift in the ratio of $PGF_{2\alpha}$ secretion to PGE_2 secretion. Intrauterine application of PGE delays the lysis of the CL (42). $PGF_{2\alpha}$ and PGE_2 exert opposing actions on the CL, and each play a critical role in luteolysis or the maintenance of a pregnancy. Estrogen secretion from the conceptus stimulates the secretion of PGE_2, a luteoprotectant, from the endometrium. Prostaglandin E_2 acts in a positive feedback

loop, which results in more PGE_2 production. This keeps prostaglandin synthesis towards PGE_2 and not $PGF_{2\alpha}$ (43).

IFNτ gene has 595 bp open reading frame, which encodes a 195 amino acid pre-protein containing a 23 amino acid signal sequence and is cleaved to yield the mature protein. The IFNτ genes expressed by ruminant conceptuses share approximately 70% homology with IFN-w. It shows remarkable homology of cDNA nucleotide sequence across ruminant species. Bovine, ovine and caprine IFNτ are more similar in sequence to each other than bIFN-t is to bovine IFN-w. Up to this date, 18 naturally occurring ovine IFNτ variants and 12 bovine IFNτ variants have been deciphered by genomic and cDNA screening (44). The ovine and bovine IFNτ molecules exhibit approximately 90% identity at the nucleotide level and 80% identity at amino acid level. IFN-tau (type 1 trophoblast interferon) has been found to abrogate uterine production of luteolytic pulses of $PGF_{2\alpha}$ by inhibiting the synthesis of endometrial ER and OTR and stabalize or upregulate PR to extend the progesterone block and prevent endometrial synthesis of OTR and/or ER. As a member of the Type I IFN family, IFNT stimulates transcription of IFN stimulated genes (ISGs) that appear to play roles in endometrial differentiation and conceptus implantation during early pregnancy (45). IFNT utilizes the classical JAK-STAT cell signaling pathway used by all Type I IFNs. All cell types in the endometrium have IFNA receptor 1 (IFNAR1) and IFNA receptor 2 (IFNAR2) with highest expression in the uterine LE (46). Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) constitutively associate with cytoplasmic domains of IFNAR1 and IFNAR2 (47). After phosphorylation of signal transducer and activator of transcription (STAT) 1 and 2, they form homodimers of STAT1 (GAF) and heterodimers of STAT1 and STAT2. These dimers translocate to the nucleus. GAF binds to the gamma activation sequence (GAS) to transactivate genes containing GAS elements, such as IFN regulatory factor 1 (IRF1). Heterodimers of STAT1 and STAT2 bind to IRF9 to form ISGF3 and transactivate genes containing IFN stimulated response elements (ISRE) including STAT1, STAT2, IRF9, B2M, ISG15, MHC and OAS (48).

Nutritional stress on embryonic survival

Nutrition plays an important role in maintenance and establishment of pregnancy in ruminants. Cows have less embryo mortality if they are gaining condition, while those losing condition will tend to have higher losses. Dunne et al. (49) showed that sudden reductions in dry matter intake (DMI) around the time of AI adversely affected embryo survival in heifer dam. When energy intake was reduced from twice maintenance to 0.8 times maintenance for 2 weeks immediately after AI, embryo survival rate in heifers was consistently less than 40%. When heifers were provided with either a constant level of feed intake or changed from a lower- to a higher-level feed intake, embryo survival was 65–71%. Following parturition, the nutrient demands of the dairy cow have been found to increase dramatically as peak lactation yield is approached and typically exceed dietary intake, resulting in a state of negative energy balance (NEB). High-producing cows of high genetic merit experience greater NEB in early lactation under grazing conditions than cows of lower genetic merit (50). Undernutrition reduces the number of follicles that emerge and therefore the number available to ovulate (51). Studies using Booroola Merino ewes showed higher ovulation rates in carriers of the FecB fecundity gene following an increased starch diet for three weeks prior to ovulation, but this increase did not occur in non-carriers of the

gene (52). Several studies report a greater number of follicles of larger diameter, in high liveweight or high BC ewes compared with low liveweight/BC ewes (53). In ewes fed 2 M diets for 6 days before and during the emergence of the ovulatory wave, increased concentrations of glucose, insulin and leptin were associated with increased numbers of follicles growing from 2 to 3 mm (54). Rhind and McNeilly (55) reported smaller follicles (1–2.5 mm) in higher intake (ad libitum) than in lower intake ewes (M). Adams et al. (56) observed that nutritionally restricted ewes exhibited slower secretion of oestrogen, due to a reduced rate of metabolic clearance of oestradiol, which may explain the higher peripheral plasma oestradiol levels observed in undernourished ewes (57). Primiparous sows were fed a restricted diet (approx. 50% maintenance) during the last week of a three-week lactation and were observed to have an embryo mortality that occurred by day 30. Following the mating of the restricted sows was largely a consequence of the death of female embryos (58).

Nutrition affects the quantity of oocytes that ovulate, in addition to, the quality of oocytes. The level of nutrition (energy content) an animal receives has the potential to influence their oocytes' developmental competence, and subsequent embryo viability in a direct and⁄or indirect way. The effect of nutrition on oocyte quality is dependent on the body condition of the animal (59). A high plane of energy intake demonstrated to be beneficial to oocytes from lean animals, while it was detrimental to oocytes from animals of moderately high body condition. The underlying mechanism includes changes in progesterone, oestrogen, IGF and insulin concentrations, and alterations in the follicular and uterine microenvironment. The high-energy diets were found to be beneficial for oocyte quality in the early postpartum period (60, 61). When the dairy cows regained a positive energy balance during the postpartum period, a (excessively) high intake of nutritional energy may have resulted in the production of over stimulated but inferior quality oocytes (62) and significantly reduced embryo quality. This may ultimately lead to decreasing conception rates, and to a higher incidence of embryo mortality. Feeding ewes 0.5 maintenance requirements for two weeks has been found to alter the relative abundance of transcripts involved in oocyte metabolic activity (63). The short-term nutrient restriction reduced expression of glucose transporter 3 (SLC2A3), sodium/glucose co-transporter 1 (SLC5A1) and Na þ /K þ ATPase mRNA in oocytes, while expression of PTGS2, HAS2 and the leptin receptor long form was increased in granulosa cells. Supplemental dietary fat has been found to increase the size and estradiol production of the pre-ovulatory follicle (64) via the induction of high cholesterol concentrations in follicular fluid and plasma. This increased follicle size may have beneficial effects on both oocyte quality and CL function (65). The hypercholesterolaemia promotes developmental competence of early embryo progesterone secretion (66). Furthermore, supplementation of polyunsaturated fatty acids can reduce prostaglandin secretion by the endometrium, in order to, support the lifespan of the CL (67), a benefit for embryo survival.

Both overfeeding and undernutrition are detrimental for embryo development. Rhind et al. (68) observed an increased rate of ova wastage in ewes that had a restricted food intake (0.5 M) compared to ewes with adequately feeding (1.5 M) during 14 days prior to mating until slaughter (11 days after mating). In sheep, ewes that were fed 60 percent of control rations for eight weeks prior to oocyte collection had poorer quality oocytes and lower rates of blastocyst formation (69). Increased pre-mating feed intake in pigs (70) and feeding a high-fibre diet to gilts during

the oestrous cycle preceding mating (71) were found to be associated with improvements in embryo survival. A reduction in the rate of embryo development and viability of embryos collected on day 2 after fertilization was observed with increasing donor feeding level during the period of oestrous synchronization (72) suggesting that nutrition during oocyte maturation has important effects on embryo viability in superovulated ewes. Abecia et al. (73) observed a delay in the development of embryos collected from undernourished ewes 8 days after mating. Abecia et al. (74) reported significantly less embryos collected from restricted ewes reaching the stage of elongated blastocysts, even though no differences in the number of blastocysts were recorded on day 9 of pregnancy. High-fibre diet prior to mating increased litter size in pigs (75) while modifications to the diet such as supplementation with dextrose during the weaning to oestrus interval (76) or feeding diets that induced a modest reduction in circulating retinol concentrations during the first month of pregnancy (77) reduced within-litter variability in piglet birthweight. The intake of high dietary protein can result in elevated blood concentration of ammonia, urea or both, depending upon the balance of protein fractions present in the rumen and the availability of fermentable carbohydrates. High crude protein levels in the diet has been found to reduce the conception rates (up to 30% and 20% decrease in lactating cows and heifers, respectively) in animals with serum urea nitrogen concentrations exceeding 20 mg⁄dl (or milk urea nitrogen concentrations >19 mg⁄dl; 78, 79). Feeding ewes with an excess of degradable protein intake (twice the requirements) during an oestrous cycle has been found to impede embryo transport on day 5 and subsequent acceleration in embryo transport and development through the oviduct (80). Higher plasma urea concentrations have been observed to interfere with the normal inductive actions of progesterone on the microenvironment of the uterus. Thus thereby causing suboptimal condition for support of embryo development (81). Endometrial cells when incubated with urea secreted significantly higher amounts of $PGF_{2\alpha}$ compared to control (81). Fahey et al. (82) found reduced embryo quality in donor ewes fed high-protein diets the diet of the embryo recipients had no effect on survival of transferred embryos. Oocytes recovered from beef heifers that experienced elevated ammonia concentrations, both in serum and in follicular fluid, showed a compromised developmental competence in vitro (83).

The establishment and maintenance of pregnancy results from molecular dialogue between the developing conceptus and maternal uterus; this molecular dialogue must be established during the peri-implantation period for pregnancy recognition signaling in ruminants. Progesterone is the main steroid hormone synthesized by CL and plays a major role in preparing the uterus for pregnancy by promoting and controlling the secretion of uterine proteins and growth factors, the growth rate of embryos, and the embryonic secretion of interferon-tau. Under-nutrition has been found to reduce the rate of secretion of IFNτ and increase production of PG from the endometrium (84). The reported pregnancy rate was low due to nutrition-induced alteration in signals of maternal recognition of pregnancy. A low energy diet during early embryo development in superovulated ewes has been observed to increase production of $PGF_{2\alpha}$ leading to a poor uterine environment, thereby compromising the development of the embryo (85). de Brun et al. (86) reported that undernourished ewes had greater *PGR* expression in the oviduct but lower expression of *IGF1* in uterus and of *IGF2* in oviducts. Sosa et al (87) studied the effects of under-nutrition on the binding capacity, immune-reactivity and mRNA expression of endometrial ER and PR in non-pregnant ewes fed either 1.5 M or 0.5 M and observed that

constraining nutrition to half the requirements for maintenance has reduced the binding capacity of both ER and PR on Day 5 after estrus. Under-nutrition affects the survival of embryo by inducing changes in the endometrial sensitivity to steroid hormones at early stages of pregnancy.

A high proportion of embryonic loss occurs in association with the period of embryonic inhibition of uterine $PGF_{2\alpha}$ secretion and suggests that some loss may be occurring because certain embryos are unable to inhibit secretion of $PGF_{2\alpha}$ (88). Polyunsaturated fatty acids such as linoleic (C18:2n-6), α-linolenic (C18:3n-3), eicosapentaenoic (EPA; C20:5n-3) and docosahexaenoic (DHA; C22: 6n-3) acids have been found to affect reproductive function and fertility. Linoleic acid is found mainly in oilseeds, whereas α-linolenic acid is found predominantly in forages and in some oilseeds (e.g. flaxseed); Eicosapentaenoic and docosahexaenoic acids are high in fish oils (FO). EPA and DHA can be supplied only by the diet because they cannot be synthesized de novo in mammalian systems. Dietary fatty acids (FO contained 36% EPA and 28% DHA) given during the periparturient period can reduce the uterine secretion of PGF2*α* in lactating dairy cows and alter the fatty acid profile of milk fat (89). Feeding fish meal, which contained approximately 8% FO (DM basis), to lactating multiparous cows for 47 to 51 d reduced the secretion of $PGF_{2\alpha}$ induced by estradiol and oxytocin injected on d 15 of a synchronized estrous cycle (90). Infusion of ewes with 3 mL/kg of BW per day (i.v.) of an emulsion of FO containing 30% EPA and 20% DHA blocked a betamethasone-induced increase in plasma concentrations of prostaglandin E_2 and delayed occurrence of parturition in sheep (91). EPA and DHA had been found to inhibit secretion of $PGF_{2\alpha}$ in different animal cell culture systems (92), including bovine endometrial cells (93). Inhibiting uterine secretion of $PGF_{2\alpha}$ in vivo by feeding EPA and DHA may reduce endometrial secretion of $PGF_{2\alpha}$ to possibly induce an antiluteolytic effect during early pregnancy and increase fertility rates (94, 95).

CONCLUSION

This review has highlighted the impact of nutritional stress on the developing oocyte, early embryo and endometrium during early pregnancy. Reduced oocyte and embryo quality are the two key players in low conception rates and in the high prevalence of early embryonic mortality. Alterations in the quantity of food consumed or the composition of the diet imposed solely during the pre-mating period has been found to affect oocyte maturity, blastocyst yield, prenatal survival and the number of offspring born alive. Until we understand the impact of nutritional stress on complex interaction between the conceptus and its maternal environment, it will not be possible to achieve major reductions in embryonic growth retardation and mortality. Improved understanding of the impact of nutrition on follicular growth, oocyte quality, and development of embryos to the blastocyst stage, endometrial function and pregnancy rate will facilitate the development of strategies and paradigm to ameliorate early embryonic losses.

Abbreviations: PGF2alpha ($PGF_{2\alpha}$), artificial insemination (AI), interferon-tau (IFNτ), maternal recognition of pregnancy (MRP), corpus luteum (CL), progesterone (P_4), estradiol (E_2), progesterone receptors (PR), estrogen receptor (ER), oxytocin receptor (OTR), endothelin-1 (ET-1), IFN stimulated genes (ISGs), IFNA receptor 1 (IFNAR1), IFNA receptor 2 (IFNAR2), Janus kinase 1 (JAK1), tyrosine kinase 2 (TYK2), signal transducer and activator of transcription (STAT), gamma activation sequence (GAS), IFN regulatory factor 1 (IRF1), IFN stimulated response elements (ISRE), dry matter intake (DMI), negative energy balance (NEB), glucose transporter 3 (SLC2A3), sodium/glucose co-transporter 1 (SLC5A1).

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