Chapter 7
Molecular Insights of Compromised Female Reproduction in Ruminants Under Metabolic and Nutritional Stress

S. Nandi, S. K. Tripathi, P. S. P. Gupta, and S. Mondal

Abstract The global increase in population and increased demand for livestock have made stress responsive decline in fertility (Metabolic stress and unbalanced diet feeding condition) a major challenge for the livestock industry. Metabolic stressors negatively affect the growth and development of ovarian cells and lead to reduced infertility in animals. Fertility in animals mainly categorized into two part one inherent property and second reproductive ability of animals which totally depends upon the feeding behaviour of animals. Stress negatively affects reproductive hormones. Reduced LH concentration associated with reduced estradiol secretion causing reduced fertility in animals by declined ovarian activity. Stress impaired folliculogenesis and ovulation process in animals. Metabolic stressors significantly altered the reproductive health of ruminants by alteration in biochemical composition of serum which directly and/or indirectly reflect in follicular, oviduct and uterine fluidresulting hampered reproductive health of ruminants. Relationship between diet and reproduction, and their interaction has long been understood to have important implications for reproductive success. The high level of urea (protein metabolites) alters glutamine metabolism and probably the function of the TCA cycle.

Non-enzymatic and enzymatic antioxidants, enzymatic cleansing is more effective. Antioxidants, like vitamins A, C and E and superoxide dismutase, glutathione peroxidase, catalase, glutathione S-transferase, peroxiredoxin and thioredoxin help cells from damaging effect of reactive oxygen species against the metabolic stress.

Keywords Antioxidant · Metabolic stress · Amelioration · Oocytes · Granulosa cells · Ruminants

S. Nandi (✉) · S. K. Tripathi · P. S. P. Gupta · S. Mondal
ICAR-National Institute of Animal Nutrition and Physiology, Bangalore, India

V. K. Yata et al. (eds.), *Sustainable Agriculture Reviews 57*, Sustainable Agriculture Reviews 57, https://doi.org/10.1007/978-3-031-07496-7_7

7.1 Introduction

The inability to achieve pregnancy is known as infertility (Adams et al. 2012). Anovulation is a potential cause of infertility in mammalian females. Attributed to poor control of the hypothalamic-pituitary-gonadal axis, endocrine hormone imbalances commonly lead to ovulatory disorders (Fig. 7.1), which account for infertility. Identifying what affects the ovulation process and recognizing what could happen with the complicated folliculogenesis or atresia process would encourage novel solutions to improve female fertility (Abedal-Majed and Cupp 2019). In addition, a deeper understanding of the biochemical processes that regulate the production of ovarian follicles and contribute to the development of a matured egg within a follicle would enable animals and women to have much more optimized assisted reproductive technologies (Allan et al. 1998; Abedal-Majed and Cupp 2019).

A stressful situation or stressor is a phenomenon outside the body that serves to decimate the body system (Lucy 2019). It is possible to quantify a stress condition and apply it uniformly across species. A strain is the reaction of the individual (the intensity of the displacement) to stress. Strong health is an unambiguous objective for farmers which are necessary for optimising animal production and well-being (Starkey et al. 1995; Pearson et al. 1997; Wilkanowska and Kokoszyn'ski 2015). Attentiveness in the care of animals has boosted over the past few decades. Wellbeing

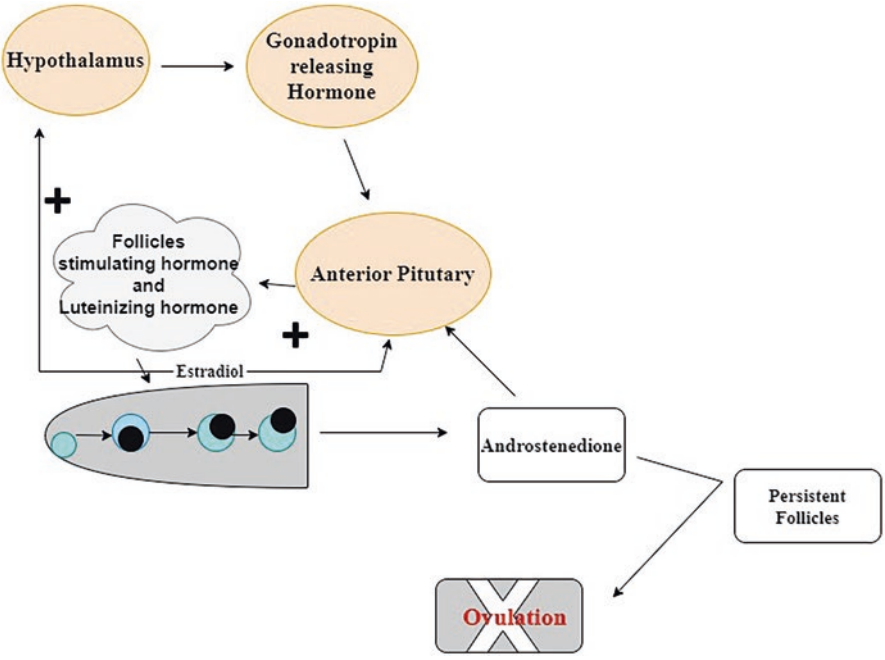

Fig. 7.1 Conceptual model of how androstenedione affects the normal hypothalamic–anterior pituitary–ovarian axis resulting in anovulation

has become the focus of many studies performed on cattle, pigs, sheep and poultry (Carlsson et al. 2007; Popescu et al. 2009; Carenzi and Verga 2009). In addition to making it possible to advance the conceptuality of the animals behaviourism, these experiments often provide a realistic view of how mammals interpret and how biological influences can impact their welfare globally (Carenzi and Verga 2009). According to Eler et al. (2002) with several components, reproduction is a complex process, some of which have been used as reproductive efficiency metrics. However, rather than by the successfulness of gestation, associated features can't be calculated easily in mammals (Eler et al. 2002). When management and nutritional conditions are optimum, most animals will reproduce, on the other hand, folks with thesuperior genetic characteristics will produce offspring under less favourable conditions (Morris 1980).

Several attributes, like physiological, surroundings environs and food intake are hypothesized to upset the reproductive profitability of animals (Wilkanowska and Kokoszyn'ski 2015). Health and dietary aspects are the most important, in relationships with their strong stimuluson reproductive capacity of livestock/animals (Smith and Somade 1994; Smith and Akinbamijo 2000; Bindari et al. 2013). In addition, more than any other, nutritional variables are readily manipulated in order to ensure beneficial results (Smith and Somade 1994; Smith and Akinbamijo 2000).

This chapter is an attempt to cover in details the effect of metabolic and nutritional stress on the reproduction of livestock, in mammals. The chapter also addresses available mitigation methods aimed at preserving livestockreproduction, in addition to these factors.

7.2 Nutrition and Reproductive Efficiency

Nutrition plays vital role in the sustaining animal reproductive performance. While genetic improvement has increased animal production, high producing animals (HPA) have also experienced a decrease in fertility at the same time. One of the main problems in HPA is reduced fertility. A network of genetic, environmental and managerial factors primarily influence the fertility of HPA, and their complex interactions make it more difficult to ascertain the exact reason for this decline (Ibtisham et al. 2017, 2018). Relationship between diet and reproduction, and their interaction has long been understood to have important implications for reproductive success (Nandi et al. 2015, 2016). In preserving the body condition and reproductive ability of dairy animals, nutrition plays a crucial role (Hoedemaker et al. 2009; Tripathi et al. 2016a, b).

Energy is particularly the key nutrient required by animals and any kind of discrepancy in the energy consumption has a deleterious effect on dairy cow reproductive activity. Energy deficiencies delay the initiation of estrus and decreases fertility in animal, as growth and follicular maturation are unsatisfactory during the Negative Energy Balance (NEB), ensuing in feeble estrus sign and diminish the likelihood of a large proportion of animal having initiated oestrus cycles for further breeding.

During the early postpartum phase, high-yielding animals (ruminants) face metabolic stress. This lead to negative energy balance (NEB) caused by the loss of energy through the processing of milk which cannot be substituted by the intake of energy (Rukkwamsuk et al. 1999; Walters et al. 2002; Ardema et al. 2013; Nandi et al. 2016). It is assumed that the negative energy balance would affect the fertility of ruminants (Walters et al. 2002; Britt 1992; Butler 2003; Tripathi et al. 2016a, b; Nandi et al. 2016, 2017). Significant body fat mobilisation raises the concentration of free fatty acid {Non-esterified fatty acid (NEFA) andbeta-hydroxy-butyrate (BHB)} in blood, follicular (Leroy et al. 2005, 2008; Nandi et al. 2016; Farman et al. 2015, 2018), oviduct and uterine fluid (Tripathi et al. 2016a, b) during times of metabolic stress.

Related to the vitality needed for upkeep and lactation, the energy costs of synthesizing and secreting hormones, ovulation and nurturing an early fertilized embryo are presumably modest. On the other hand, the biochemical manifestations connected with NEB prejudice the re-establishment of oocyte growth and production, and successfully pregnancy achievement as well as retention in dairy cattle. These results in severe economic loss to the dairy industry due to sluggish uterine involution, abridged reproductive performance, and calving durations, detrimental impact on productiveness, improved drug costs, reduced production (milk), reduced veal crops and early amortization of highly helpful livestock. Short or long term shortage cause result in under feeding. Animals with unbalanced feeding behaviour are stressed and attempt toendure metabolic revision to the stress [lipid mobilization and non-esterified fatty acid (NEFA) release] (D'Occhioet al. 2019). Obesity linked through insulin resistance, and the body storage (adipose mass) is less responsive in controlling effects of insulin. Therefore, obesity impair the brutality of metabolic ailments by the establishment of vicious response that lead to heightened lipolysis and amplified non-esterified fatty acid and beta-hydroxy-butyrate concentrations in circulation. Even though the effect of fatness prompted insulin resistance is not well-known in animals, few study demonstrating that this may be the case and disproportionate body fat is a well-known encouraging threat for metabolic related abnormalities in animals.

Dietary status is a key factor that influences the ability of an animal to produce (O'Callaghan et al. 2000; Tripathi et al. 2016a, b). Embryo viability has been related to nutritional status and is a vital factor affecting proficiency in assisted reproductive technologies (ART) (Webb et al. 2004). Feed intake and subsequent nutritional prominence may affect animal's fertility (Bridges et al. 2012). The perceptible measure of metabolic health is the body condition score (BCS) and continuous variation in it is used to analysethe state of animals (nutritional and physical) mostly for production (Berry et al. 2007). Body condition score (BCS) is correlated both phenotypically and genetically with reproductive success (Kubovicova et al. 2013). Found that high body condition score and/or adipose animal showed considerably elevated concentration of glucose on the day of birth than with ideal circumstance. Moreover, amount of glucose (sugar) substantially declined next 12 days. Most possible reason might be because of lower appetite in animals after parturition resulting

high negative energy balance. Farman et al. (2018) also reported low blood glucose concentration in metabolic stressed ewes.

Disproportionate lipolysis during the early lactation associated with numerous reproductive abnormalities along with placental retention, and endometritis and reduced mRNA expression of immune; growth and development related gene in the endometrium. The effect of fertility and lipid metabolism in bovine are studied strongly, moreover, exact mechanisms responsible for the negative effect of lipolysis on animals fertility must be solved. Before and after pregnancy (transition period) and the commencing of lactation, white adipose tissue is the chief organ accountable for fat deployment and subsequently for alteration in non-esterified fatty acid concentration prompted by the negative energy balance in animals. Nutrition play vital role in determining the reproductive efficiency of animals. Unbalanced feeding significantly alter the biochemical environment of follicular fluid and/or uterine fluid, these alteration in biochemical environment reduce reproductive performance of animals by altering hormonal concentration along with changes in cell growth and development.

7.3 Metabolic Stressors and Oocyte Development and Molecular Approach

Significant but confined range of multifarious molecular structures in the ovary known as the ovarian follicles. Initially, they are formed in the form of precursor follicles residing single layer of flattened cells adjacent to the dormant oocyte. Basal cells enclose each precursor follicles, which separates the follicle throughout follicular development from the majority of the ovarian cytoplasm (Baddela et al. 2020). For months or years, most primordial follicles remain in a quiet phase before further development begins (Hirshfield 1991). Follicles with a single granulosa cells (GCs) layer are called major follicles, as well as those with numerous levels of granulosa cells layer are called secondary follicles.

It is argued that the growth of primary to secondary follicles is hormone (follicles stimulating hormone (FSH) and luteinizing hormone (LH)) responsive process. In secondary follicles, additional layers such as interna and externa cellsbegin to appear on the periphery of the basement membrane and make a significant contribution in follicular growth (Orisaka et al. 2009; Baddela et al. 2020). Gonadotropin-dependent progressive proceedings from secondary to ovulatory follicles occur as the granulosa cells triggered by stimulators like follicles stimulating hormone. Follicles stimulating hormone prompts growth and biosynthesis of hormones (steroid) in granulosa cells in combination with insulin-like growth factor 1 (IGF-1) and promotes follicular antrum development (Baddela et al. 2020). Follicular growth influenced mostly by on the animal's healthiness and vitality status, in addition to timely endocrine stimulation. Folliculogenesis has been shown to be significantly impaired during pre and post-partum condition (Tripathi et al. 2016a, b) unbalanced

feeding (High protein diet feeding) (Aardema et al. 2013; Leory et al. 2008; Nandi et al. 2018). According Valckx et al. (2014) and Nandi et al. (2016) raised on esterified-fatty acid concentrations possibly prejudice fertility, by fluctuating physiology and sinking oocyte development ability. Treatment with elevated concentration of stearic acid (SA) tended to decrease glucose absorption and depletion of mural granulosa cells (decreased mRNA expression of Slc2a1 and GAPDH gene) compared to physiological and/or high non esterified-fatty acid treatment (Baddela et al. 2020). Long-term exposures to murine follicles to elevated NEFA concentrations (720 mM) has been known to decrease follicular development, with substantial outcome triggered by elevated stearic acid (280 mM, Valckx et al. 2014).

Higher serum on esterified-fatty acid levels are linked with a decrease glucose concentration in follicular fluid (Roth 2017; Leroy et al. 2015; De Bie et al. 2017). This decrease in the amount of glucose can have a major impact on the production of oocytes because glucose is the main source of energy and responsible for the vital biological components for maturation, together with pyruvate, adenosine triphosphate (ATP), and nicotinamide adenine dinucleotide phosphate (NADPH) and glutathione that neutralize the reactive oxygen species (Sutton-McDowall et al. 2010). There is bidirectional coordination between the oocytes and the corresponding cell types. Gonadotropins stimulate meiotic oocyte commencement via triggering of the signaling pathway (EGFR) in granulosa cells (Richani 2014). Growth factors such asGrowth differentiation factor 9 (GDF9), Bone morphogenetic protein 15(BMP15), and Fibroblast growth factor 8 (FGF8B) also regulate the role of granulosa cells (Emori and Sugiura 2014). Nutritional factors may influence reproduction separately or in combination, at the level of the hormones production, oocyte growth and embryo uterus interaction (Bilodeau-Goeseels and Kastelic 2003). Oocytes resulting from follicles subjected to stress (environmental and metabolic stressors) have reduced reproductive fitness (Nabenishi et al. 2012; Gebremedhn et al. 2020), accompanied by reduced fertilization ability and blastocyst stage development and establishment of pregnancy (Roth and Hansen 2005; Gebremedhn et al. 2020). The association between both the oocyte and the biochemical environment is affected by exposure to stress. Communication between follicle and the oocyte is predominantly befell by paracrine and autocrine molecules via gap junction and/or by discharge of molecules (Bosco et al. 2011; Gebremedhn et al. 2020).

The recent developments and characterization of vesicles derivedfrom different types of cells represent eminent cell communication mechanism (Yáñez-Mó et al. 2015). In transporting biomolecules like mRNAs, miRNAs, and proteins, EVs significantly indicate the physiological status of the origin of cells (Valadi et al. 2007a, b; Silva and Melo 2015; Gebremedhn et al. 2020). EV is characterized by the existence of unique membrane proteins, along with clusters of differentiation −9, 63 and 81 (CD9, CD63, CD81), tetraspanins and additional proteins such as: ALIX and TSG101 (Kumar et al. 2015). EVs have been reported to be present in bovine (Hung et al. 2015; Hailay et al. 2019a, b), equine and human follicular fluids and are necessary for transporting biomolecules (RNA, miRNA) during growth and development of follicles (da Silveira et al. 2012; Santonocito et al. 2014). During early lactation, high producing animals underwent a state of conditions known as negative energy

balance. This in fact, outcomes in fluctuations in the amount of different biomolecules in the microenvironment of the body and follicular fluid (Farman et al. 2018) and oviduct/uterine fluid (Tripathi et al. 2016a, b) which lead to disrupted fertility. In cell-to-cell contact, extracellular vesicles play a critical role and hold a large number of biomolecules that can be supplied to act in other cells (Valadi et al. 2007a, b). Thousands of exosome-mediated molecules, including around 9769 proteins, 3408 mRNAs, 2838 miRNAs, and 1116 lipids, have been reported (Keerthikumar et al. 2016). Animals with negative energy status in the displayed exclusive expression of eight miRNAs, five of which were located on chromosome 21 (bta-miR-431, bta-miR-370, bta-miR-136, bta-miR-376e and bta-miR-411c-3p) (Hailay et al. 2019a, b). A strong correlation between metabolic stress and the release of Extracellular vesicles-coupled miRNAs was revealed by hierarchical clustering of differentially expressed Extracellular vesicles (EVs)-coupled miRNAs between cows with divergent metabolic states (Hailay et al. 2019a, b).

MiR-21, believed to be active in follicular development. High expression of MiR-21 in mice related with better subsistence and ovulation (Christenson 2010). In regulating maternal-to-embryonic transfer and early growth, increase expression of miR-21 was involved (Mondou et al. 2012). Thus in the research analysis, the downregulation of EV-coupled miR-21 due to metabolic stress can indicate a corresponding reduction in follicular cell expression, that could hinder follicular growth. Additionally, accelerated miR-20b transcription in bovine CCs (cumulus cells) high maturation rate and production of progesterone by pointing INHBA, MAPK1, PTGS2, PTX3, and EGFR55 (Andreas et al. 2021; Hailay et al. 2019a, b). The molecular analysis of the package of EVs with a possible influence on the development of oocytes and embryos responsible for the development of bio- markers for the implementation of systems for addressing infertility. The components of Extracellular vesicles (EVs) produce from granulosa cells and oviductal epithelial cells in response to stress are defined (Gebremedhn et al. 2020). By upsetting steroid synthesis, cell growth, and cell apoptosis essential for follicles growth, fatty acids have been described to amend granulosa cells functions (Elis et al. 2015; Tripathi et al. 2016a, b; Nandi et al. 2018; Sharma et al. 2019). The induction of extreme morphological changes in granulosa cells is one of the anticipated effects of highernon-esterified fatty acid concentration. Yenuganti et al. (2016) and Sharma et al. (2019) conveyed the development of fizzlike cell structures in cultured bovine GCs on treatment with higher concentration non-esterified fatty acid concentration[(Oleic acid (OA), Palmitic acid (PA), and Stearic acid (SA)] in addition to the major impact on the expression of essential genes and hormone production (Nandi et al. 2018; Farman et al. 2015). Granulosa cells synthesise and synthesize sufficient quantities of estrogen after encouragement with follicle stimulating hormone and insulin growth factor −1 (IGF-1) under healthy conditions Adversarial morphological changes in granulosa cells occurred because of saturated fatty acids with an increase apoptosis rate in granulosa cells. In granulosa cells, decreased phosphorylation of Akt has been Increased expression of genes regulated by CD36 (fatty acid transporter), insulin growth factor −1 and follicle stimulating hormone reported in granulosa cells (Hailay et al. 2019a, b).

Ammonia is unfavorable for embryo development. Urea negatively affect the oocyte by need of amino acid, and overall amino acid loss and turnover at higher amount (Kowsar et al. 2018).“Exhaustion of essential amino acids (EAAs) (histidine, tryptophan, lysine, isoleucine and leucine), semi-essential amino acids (serine, arginine and glutamine), and non-essential amino acids (ornithine and aspartic acid)” was increased by elevated urea concentration (Kowsar et al. 2018). Hemming et al. (2012, 2013) observed that in incompetent oocytes the overall turnover and loss of amino acids was greater than their split counterparts. Dynamic genetic assortment combined with feeding high protein diets to upsurge milk production which was accompanying with declined fertility in animals. The high level of urea will alter glutamine metabolism and probably the function of the TCA cycle (Kowsar et al. 2018).

Elevated urea concentration is responsible for increase lysine turnover. Kowsar et al. (2018) reported that elevated urea concentration, significantly washed-out more lysine and methionine in cumulus oocyte cells complex (COCs) and DOs (Denuded oocytes), which is the most limiting amino acid in dairy animals during lactation (Schwab et al. 1992). Urea considerably declined the viability of epithelial cells in oviduct (Kowsar et al. 2016). The viability of cumulus cells cumulus oocyte cells showed a negative correlation with alanine turnover (Kowsar et al. 2018). Alanine has been recognized as a marker of apoptosis, with an increase in its concentration in apoptotic cells (Halama et al. 2013). This suggests a relationship between lower viability of cumulus oocyte cells and greater alanine appearance (Kowsar et al. 2018). Several studies reviewed about the impact of metabolic stressors [NEFA, BHB, and protein metabolites (ammonia and urea)] in oocyte maturation and development as mentioned in Table 7.1.

Animals with declined levels of insulin growth factor-1 in serum collected after parturition, showed endometritis than animals with normal insulin growth factor-1 concentrations. Mattiauda et al. (2017) reported, the higher transcript expression of insulin growth factor-1 in total mixed ration and high grazing animals than medium grazing animals and lower grazing animal) cows— animals with enhanced nutritional grade during lactation, for example, indicate a favorable uterine environment for the development of embryos. Progesterone stimulates the growth of the embryos and contributes to the secretion of interferon gamma (IFNÿ) by acting on the endometrium and resulting release of various embryotrophic factors. In fact it was shown that transcript expression of insulin growth factor-1 is predominantly controlled by the action of progesterone on the endometrial uterine.

Reproductive tract environment is not only affected by physiological processes of reinforcement, inflammation and infection but also by the metabolic condition of the animal. An earlier study found altered gene expression of insulin growth factor binding protein in cow oviducts with negative energy balance; however, the influence of changes in gene expression on embryo development was not analysed. During the dry and postpartum cycle, it seems that feed restriction generally influences global gene expression in the oviduct. Therefore, it’s important to consider the ruminant’s physiological condition in studies that further scrutinize the root causes for reproductive disorders. Fatty acids were also suggested as key midstream

Table 7.1 Studies of metabolic stress and nutritional stress in in-vitro fertilization (IVF)

Animal	Experimental findings	References
Bovine	Elevated non-esterified fatty acid (NEFA) concentration, responsible for epigenome alterations in matured oocyte or in embryo. Cell survivability, invulnerability, metabolic rate are associated with major impaired pathways.	Desmet et al. (2016)
Bovine	Low cell numbers in blastocyst, augmented apoptosisrate and altered gene expression (DNA Methyltransferase 3 Alpha, Insulin Like Growth Factor 2 Receptor and Solute Carrier Family 2 Member 1) resulted in maturation in elevated non-esterified fatty acid concentrations. Additionally the blastocysts showed declined consumption of oxygen, and glucose, higher lactate consumption and metabolism of amino acids.	Van Hoeck et al. (2011)
Cattle	By increasing the expression of endoplasmic reticulum stress marker genes: activating transcription factor 4 and heat shock protein family A (Hsp70) member 5, higher non esterified fatty acid concentrations at maturation provoke endoplasmic reticulum stress in cumulus..	Sutton-McDowall et al. (2016)
Mouse	Feeding high fat diet and exposure of oocyte to elevated lipid responsible for increased expression of activating transcription factor 4 and heat shock protein family A (Hsp70) member 5, in mouse COCs.	Wong et al. (2015)
Bovine	Expression of glutathione peroxidase-1 (reduced glutathione to oxidized glutathione) in oocyte, has been declined by non-esterified fatty acid supplementation.	Van Hoeck et al. (2015)
Ovine	Metabolic stressors repressed granulosa cells proliferation, increase apoptosis rate, declined hormones production rate, and reduced steroid-related gene expression. The expression ofapoptosis related geneBCL-2 and BAX were significantly increased in higher levels of metabolic stressors, ratio of BAX: BCL2 ratiowas significantly in higher elevated level of metabolic stressors.	Nandi et al. (2018)
Human	Unsaturated fatty acid significantly reduce the transcript expression of BAX and encourage BCL2 and transcript expression in GC	Valckx et al. (2014)
Bovine	Unsaturated fatty acid lower the transcript expression of genes Steroidogenic Acute Regulatory (STAR), Cytochrome P450 Family 19 Subfamily A Member 1 (CYP19A1), Follicle Stimulating Hormone Receptor (FSHR), Cytochrome P450 Family 11 Subfamily A Member 1(CYP11A1), Cyclin D2 (CCND2) and Proliferating Cell Nuclear Antigen (PCNA).	Sharma et al. (2019)
Ovine	Ammonia (250 μM and 150 μM) negatively affectgrowth and secretary activity of granulosa cells isolated from small and/or medium follicles and large follicles respectively.	Nandi et al. (2016)
Bovine	Supplementation of elevated concentration of ammonia and urea on bovine endometrium cells *In vitro* significantly reduce the mRNA expression of Insulin Like Growth Factor Binding Protein 1and Fibroblast Growth Factor 2 (FGF2). However, moderate concentration of ammonia and urea significantly increase the mRNA expression of Heat Shock Protein Family A (Hsp70) Member 1A (HSPA1A), Insulin Like Growth Factor Binding Protein 3 (IGFBP3) and Serine Protease Inhibitor-14(SERPINA14) genes.	Gunaretnam et al. (2013)

regulatory agencies of modifications in genome sequences detected in trophectoderm cells when elongation started. Consequently, sufficient concentrations of peroxisome proliferator-activated receptor gamma (PPARÿ) fatty acid ligands in the histotrophics result in increased transcription factor activity and subsequent alterations in cell environment necessary for conceptual elongation. Additionally, due to inadequate concentrations of peroxisome proliferator-activated receptor gamma fatty acid ligands or inconsistent fatty acid profile in the histotrophic slow down conceptus elongation which lead to a loss of pregnancy. These theory are endorsed by the significance of peroxisome proliferator-activated receptor gamma in trophoblast and placenta in mice, humans and sheep. For example, the genetic ablation of PPARÿ in mice resulted in embryonic lethality due to placental inefficiencies.

After parturition negative energy balance last to 70–84 days (10–12 weeks), during this period of time in animal fertility is reduced (Butler 2003). After examining the biochemical environment in the serum and follicular (Leroy et al. 2005; Nandi et al. 2013; Farman et al. 2015) oviduct and uterine fluid (Tripathi et al. 2016a, b) found that its administration of metabolic stressors (NEFA, BHB, ammonia and urea) to the cell culture decreases ovarian cells (granulosa cells, and oocyte) and endometrium growth and development. Antioxidant capacity decreased during stress in mammals (Ferreira et al. 2016). In addition, oocyte and embryo exposed to HS in vitro, elevated concentration of reactive oxygen species (ROS) impairs embryo development (Sakatani et al. 2004; Roth 2017). In addition, Van Hoeck et al. (2013) and Nandi et al. (2018) reported that metabolic stressors induced oxidative stress is responsible for reducing growth and development of oocyte in animals suffering from negative energy balance. Furthermore, animals displaying signs of negative energy balance and imbalanced feeding-(loss of body weight, elevated NEFA and BHB, ammonia and urea levels)-have oxidative stress (Tripathi et al. 2016a, b), which can be explained by decreased concentration of antioxidants (β-carotene, vitamins C and E, superoxide dismutase, and glutathione peroxidase) in serum and in follicular fluid. After pregnancy has been developed, ROS negatively affect the placenta and soon or later fetus survival, with consequences for the pathophysiology of abortion, impulsive membrane rupture and fatal disease.

Oocyte production affected by extrinsic oxidative stress parameters present in metabolically compromised mothers' follicular fluid, but also by intrinsic oxidative stress in the oocyte caused by exposure to extrinsic oxidative stress and/or altered metabolic factors. In the peritoneal fluid of endometriosis patients significant elevation in the concentration of oxidative stress markers, particularly lipid peroxides (LPO), was observed. Additionally, women with endometriosis reported that the peritoneal fluid contains low levels of antioxidant. In addition to the correlations described above, glutathione peroxidase (GPx) and total antioxidant status (TAS) levels in follicular fluid have been shown to be higher, achieving efficiently and effectively fertilized oocytes than non-fertilized oocytes in follicular fluid. In conclusion, metabolic stressors (NEFA, BHB, ammonia and urea) significantly alter the growth and development of oocyte by significant alteration at gene level. Metabolic stressors increased the reactive oxygen species concentration leads to reduced growth of cells; metabolic stressors significantly lowered the mRNA expression of growth related gene.

7.4 Strategies to Ameliorate the Negative Effect on Reproduction During Metabolic and Nutritional Stress

As described above, stress has a negative impact on the anti-oxidant scavenging activity of ruminants, oocytes and the subsequent embryos, so antioxidant supplementation responsible for alleviating the action against stress. Reactive oxygen species and the antioxidants were necessary for ovulation and a disproportion among them was responsible for the oocyte‘s inferior quality. While it needs both non-enzymatic and enzymatic antioxidants, enzymatic cleansing is more effective.“Antioxidants, like vitamins A, C and E and superoxide dismutase, glutathione peroxidase, catalase, glutathione S-transferase, peroxiredoxin and thioredoxin helps cells from damaging effect of reactive oxygen species” (Bettina et al. 2017). Because of the potential to inhibitreactive oxygen species, especially during the biosynthesis of steroid hormones, antioxidant enzymes within granulosa cells, cumulus cells, and follicular fluid each play a pivotal role in oocyte protection (Bettina et al. 2017). The follicular fluid acts as a buffer for antioxidant because of close proximity of the cumulus oocytes cell complex which helps in maintaining redox balance. Oxidative stress-induced DNA damage in granulosa cells is inversely related to quality of embryo and fertilization rate.

Antioxidants are useful in reducing oxidative stress, as they scavenge free radicals and decrease the amount of reactive oxygen species. Antioxidants (enzymatic and non-enzymatic) are also used to decrease reactive oxygen species and therefore the degree of oxidative stress (Sharma and Agarwal 2004; Agarwal et al. 2012; Prasad et al. 2016).“In order to resolve this problem, antioxidants such as superoxide dismutase, catalase, glutathione peroxidase and glutathione oxidase, vit C, taurine, hypotaurine, vitE, Zn, selenium (Se), betacarotene, and carotene may be useful” (Prasad et al. 2016). Animal studies have demonstrated that supplementation with antioxidants is helpful in overcoming the disadvantageous effects of oxidative stressin oocytes (Sharma and Agarwal 2004; Agarwal et al. 2012; Prasad et al. 2016). Melatonin tends to play a significant role. To sustain the production of progesterone from ROS produced during the ovulation, melatonin protects granulosa cells (Taniguchi et al. 2009). “Melatonin (N-acetyl-5-methoxytryptamine) is a drug derived from the pineal glands and peripheral nerves”. There are mainly two G protein–coupled receptors for melatonin, melatonin receptor-1 and -2. Melatonin’s antioxidant effects may protect oocytes from oxidative stress harm. Action of melatonin on oocyte is mediated by its receptors. Follicular fluid concentrations of melatonin are closely correlated with both oocyte quantity and quality. In human granulosa cells, melatonin regulates the mRNA expression of vascular endothelial growth factor (VEGF) and down-regulate Inducible nitric oxide synthaseexpression. “Melatonin, antioxidant capacity, is five times more powerful thanGlutathione and eight times more powerful than mannitol”. During the dry period under stress, melatonin enhanced production rate and decreased the rates of breeding dysfunction and disruption of pregnancy in animals.

During IVEP (in-vitro embryo production), melatonin decreases reactive oxygen species production and cellular apoptosis, improves the rate of blastocysts yield, increase the transcript expression of the super oxidase dismutase andB-cell lymphoma 2 (Bcl-2) and decrease transcript expression of p53. At the time of apoptosis cytochrome C (cyt-C) binds to Apaf-11 (has a caspase binding region) and the release of cyt- C inhibited by B-cell lymphoma 2. Reduced healthy follicles was reported in B-cell lymphoma2knockout animals and higher transcript expression of B-cell lymphoma 2gene in granulosa cells lower apoptosis rate. The existence of melatonin in follicular fluid was interrelated with oocyte number excellence and graafian follicles number, anti-Müllerian hormone (AMH) in serm, estradiol level in serum, and total number of embryos produced (Tiboni et al. 2004; Budani and Tiboni 2020). Melatonin enhanced the mitochondrial function of in vitro matured mice oocytes and protected in vitro matured oocytes against oxidative stress. Supplementation with melatonin increase mitochondrial function. Supplementation of melatonin during in-vitro maturation increases the copy number of the mitochondrial DNA (mtDNA), along with the potential of the mitochondrial membrane (Ochiai et al. 2019; Budani and Tiboni 2020). In mice, melatonin enhanced reproductive efficiency in an in vivo study conducted by Gao et al. (2012) steadily increasing melatonin concentrations in drinking water (0, 3, 30, 300 μg/mL) were exposed for 21 days to ICR mice, aged 7 weeks. A dosage of 30 μg/mL was linked to higher number of antral follicles in each region of the ovarian structure compared with control. In addition, 30 μg/mL dose of melatonin during thein- vitro fertilization significantly increased the hatching rate relative to the control group and other groups treated with melatonin. (Gaoet al. 2012; Budani and Tiboni 2020).

Vitamin E is commonly used in the field of assisted reproductive and can effectively reverse the harmful effects of oxidative stress on the reproductive system and the endocrine system. (Chen et al. 2020). Vitamin E, which is vitally important throughout the female reproductive process, can vilify oxidative damage by oxygen-free radicals and antioxidant deficiency by repressing the action of phospholipase A and lipoxygenase to sustain the cell membrane and guiding the usual physiological position of the reproductive system (Chen et al. 2020). Vitamin E can reduce the senile oxidative stress reaction with the anti-oxidant properties, which may have a negative impact on the number and quality of oocyte (Chen et al. 2020). Dairy cattle eating stored forages are often poor in vitamin E unless supplemented, and deficiencies in vitamin E are often found during the periparturial cycle leading to placenta retention and then anoestrus injection of diazinon (DZN) to rat decreases cells proliferation in secondary and Graafian follicles, supplementation of Vitamin E recover the toxic effect of diazinon. On oocytes, the impact of stress on maternal metabolic nutrition and antioxidant status is transmitted, resulting in embryos and the fertility state of the ruminant (Abdelatty et al. 2018). Long-term maternal diet programming is therefore the main factor in reducing the stress impact on the oocytes and the growth of embryos. Furthermore, adequate nutrition management of the high producing animal to preserve the energy balance can have a favorable outcome on the oocytes and the potential offspring (Abdelatty et al. 2018).

L-ascorbic acid (VitC) synthesized in the liver of many animals, with the exception of guinea pigs, human and other primates (Cantoni et al. 2017; Yu et al. 2018). Ascorbic acid was found to be strongly transported to cells by the high affinity sodium-dependent vitamin C transporters 1 and 2 to achieve a levels of 1 ~ 10 mM (Young et al. 2015;Cantoni et al. 2017;Yu et al. 2018). A complex molecular network coordinates the development of mammalian oocytes, and dynamic regulation of DNA methylation and histones is essential both for meiosis and embryonic development (Gu et al. 2010; Yamaguchi et al. 2012). Methylation (trimethylation) in histone-3(H3) at Lys-4 and Lys-36 linked with dynamicchromatin position while methylation at Lys-9 and Lys- 27 linked with suppressive chromatinstatus, which also have important evolutionary functions in the regulation of oogenesis and embryogenesis (Diao et al. 2014, 2016; Stewart et al. 2015; Yu et al. 2018.

According to outcomes of Chawalit et al. (2012) and Mallol et al. (2015) supplementation of ascorbic acid duringIVEPadvance blastocyst development rate in porcine hand-cloned embryosand mouse embryos made by SCNT (Somatic cell nuclear transfer). In porcine oocyte ascorbic acid supplementation increases meiotic maturation and developmental competence of porcine oocytes through epigenetic reprogramming (Yu et al. 2018). According to the finding of Yu et al. (2018) ascorbic acid reduces reactive oxygen species level and increase bone morphogenetic protein -15transcript level. Oxidative stress responsible for alter epigenetic status while supplementation of ascorbic acid responsible for modify epigenetic status in oocyte (McDonough et al. 2010; Young et al. 2015). During the periparturient period significant decline in concentration of vitamin C in serum was recorded in dairy cows. In lactating animal, heat stress reduced the serum Vit C concentration the serum Vit C concentration with regulated high ambient temperature decreased by 50%. In contrast, we further reported that the serum Vit C concentration in the summer was substantially lower than those in the autumn in milking animals. While H3K4me3 and H3K36me3 are typically associated with actively transcribed chromatin, H3K9me3 and H3K27me3 are associated with repressive chromatin. According to study of Hancock et al. (2015) ascorbic acid usage considerably reduced expression of H3K27me3 but higher the expression of H3K4me3 and H3K36me3 in matured oocyte.

Selenium (Se) is an effective antioxidant factor that has ruminant animal's functions, including reproductive activity of both sexes (Mehdi and Dufrasne 2016; Lizarraga et al. 2020). During early lactation cattle experienced reduced antioxidant defense capability, even with sufficient Se concentration in their rations. Selenium-yeast supplementation to Se-sufficient animals during late gestation increases serum selenium concentration, and it helps in improving antioxidant defense mechanism, and diminishes oxidative stress in early lactation. Supplementation with 10 ng/mL dose of selenium during in-vitro maturation of cattle (*Bosprimigenius Taurus)* improve embryo quality (Lizarraga et al. 2020). According to findings of several study in cow, reduced fertility, placental preservation, and augmented frequency of mastitis and metritis were linked with selenium deficiency (Spears and Weiss 2008; Hefnawy and Tórtora-Pérez 2010; Sordillo 2013). In human, supplementation of Se, calcium, and calcium ionophore to IVM medium increased the oocytes maturation

rate (Makki et al. 2012). Selenium inhibits oxidative damage and also affect the transcipt expression of the follicles stimulating hormone receptor in granulosa cells, according to Basini and Tamanini (2000). It has been shown that selenoproteins such as glutathione peroxidase and thioredoxinreductase can exert their beneficial effects through selenium (Brigelius-Flohé and Maiorino 2013). Ceko et al. (2015) confirm the presence of selenium and glutathione peroxidase −1 in large follicles of bovine granulosa cellsand play a vibrant role as anti-oxidants throughout late follicular development. Coenzyme Q10 (CoQ10) acts as a scavenger against reactive oxygen species (Asensi-Fabado and Munné-Bosch 2010). According to Dai et al. (2017) treatment with coenzyme Q-10in mouse delayed ovarian reserve depletion, regained the mitochondrial gene expression of the oocyte, and enhanced mitochondrial activity. Several findings reviewed about the significance of antioxidants in oocyte growth and development as mentioned in Table 7.2, Fig. 7.2. The supplementation of antioxidant molecules in both (*In-vitro and In-vivo*) reduces oxidative stress and it's clearly required for optimum animal performance. Optimised antioxidant feeding may increase the therapeutic efficacy of the follicular environment, irrespective of the animal metabolic stress status, the above may offer a treatment to help' the oocyte that is metabolically affected.

7.5 Conclusion

Metabolic and nutritional stress undoubtedly place stress on all livestock species and will adversely affect their reproductive capacity. The effect of metabolic and nutritional stress was addressed in detail in this segment. This chapter also elaborated on improvement measures to be taken into account in order to avoid economic losses caused by metabolic and nutritional stress pressures on livestockreproduction. Metabolic and nutritional stress conditions negatively influencedoocyte and embryo development and quality. The difficulty in implementing this nutritional strategy is the lack of awareness of particular animals' individual antioxidant deficiency, the potential role of other nutrients, and their interactions with antioxidants. This first logical step towards enhanced fertility is to enhance metabolic health. The use of antioxidants *in vitro* embryo culture support development of embryos after a metabolic praise during oocyte maturation, which improve embryo quality. Although it is important to further elucidate the degree to which these antioxidant supplementation will potentially rescue the metabolically compromised oocyte by nutritional and metabolic stress in a combined in vivo and in vitro approach.

Table 7.2 Important antioxidants and their role in ovarian physiology

Animal model	Antioxidants	Experimental findings	References
Cattle	α-Tocopherol	Responsible forthe survival of pre-antral follicles and encourages the stimulation of primordial follicles in *in vitro* culture of cattle follicles.	Lisboa et al. (2009)
Bovine	Zinc	Zinc considerably affected intracellular GSH content and DNA integrity of cumulus cells during oocyte maturation and improved pre-implantation embryo development in bovine	Picco et al. (2010)
Ovine	α-Tocopherol and ascorbic acid	In combinations significantly increase the maturation rate of sheepoocyte	Miclea et al. (2012)
Porcine	Selenium and vitamin E	Increased the maturation rate of porcine oocytes and blastocysts.	Tareq et al. (2012)
Porcine	Rresveratrol	Increase blastocyst formation rates and total cells number. Reduced mRNA expression of apoptosis-related genes in COC treated with resveratrol	Kwak et al. (2012)
Bovine	Melatonin	Reduce the negative effect of stress on bovine oocytes.	Cebrian-et al. (2013)
Bovine	Resveratrol	Improved cumulus expansion, polar body formation, hatched blastocyst rate and mean number of cells in blastocysts	Wang et al. (2014)
Porcine	Ascorbioc acid	Significantly enhanced survival rates of blastocysts and reduced peroxide levels.	Castillo-Martín et al. (2014)
Camel	Selenium, melatonin, ascorbic acid, β-mercaptoethanol etc.	Maturation medium supplemented with different antioxidants had a beneficial impact on maturation rates.	Mayada et al. (2015)
Ovine	Fenugreek seed extract (FSE)	Significantly improved the maturation of oocytes.	Barakat et al. (2018)
Human	CoQ10	Improved oocytes retrieval, higher fertilization rate, and more high-quality embryos	Xu et al. (2018)
Human	Vitamin C	Treatment via oral route accelerates the level of Vit C in serum and follicular fluid improving the quality of oocytes and embryos in IVF-ET cycles	Lu et al. (2018)
Cattle	Selenium	Improve embryo quality.	Lizarraga et al. (2020)
Bovine	Resveratrol	Attenuated the increasing in active mitochondria in embryos cryopreserved	Gaviria et al. (2019)

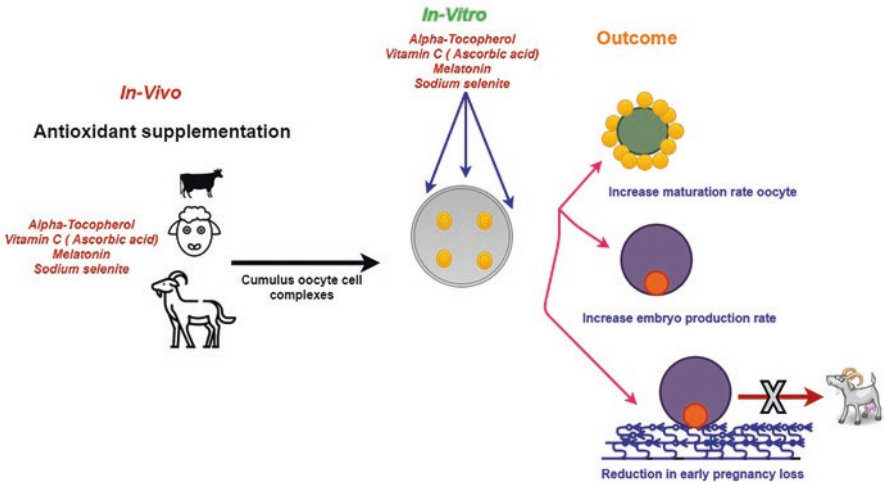

Fig. 7.2 Antioxidant administration strategies for overcoming Nutritional and metabolic stress

References

Aardema H, Lolicato F, van de Lest CH, Brouwers JF, Vaandrager AB, van Tol HT, Roelen BA, Vos PL, Helms JB, Gadella BM (2013) Bovine cumulus cells protect maturing oocytes from increased fatty acid levels by massive intracellular lipid storage. Biol Reprod. 88(6):164. https://doi.org/10.1095/biolreprod.112.106062

Abdelatty AM, Iwaniuk ME, Potts SB, Gad A (2018) Influence of maternal nutrition and heat stress on bovine oocyte and embryo development.Int. J Vet Sci Med 6(1):S1–S5. https://doi.org/10.1016/j.ijvsm.2018.01.005

Abedal-Majed MA, Cupp S (2019) Livestock animals to study infertility in women. Anim Front 9(3):28–33. https://doi.org/10.1093/af/vfz017

Adams GP, Singh J, Baerwald AR (2012) Large animal models for the study of ovarian follicular dynamics in women. Theriogenology 78:1733–1748. https://doi.org/10.1016/j.theriogenology.2012.04.010

Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A, Gupta S (2012) The effects of oxidative stress on female reproduction: a review. Reprod Biol Endocrinol 10:49. https://doi.org/10.1186/1477-7827-10-49

Allan T, Ian C, O'Brien S (1998) Evidence-based fertility treatment. Royal College of Obstetricians and Gynaecologists Press, London

Andreas E, Pandey HO, Hoelker M, Salilew-Wondim D, Gebremedhn S, Schellander K, Tesfaye D (2021) The regulatory role of miR-20a in bovine cumulus cells and its contribution to oocyte maturation. Zygote 23:1–10. https://doi.org/10.1017/S0967199420000933

Asensi-Fabado MA, Munné-Bosch S (2010) Vitamins in plants: occurrence, biosynthesis and antioxidant function. Trends Plant Sci 15:582–592. https://doi.org/10.1016/j.tplants.2010.07.003

Baddela VS, Sharma A, Vanselow J (2020) Non-esterified fatty acids in the ovary: friends or foes? Reprod Biol Endocrinol 18:60. https://doi.org/10.1186/s12958-020-00617-9

Barakat IAH, Alajmi RA, Zoheir KMA, Salem LM, Al-Hemidiy AR (2018) Gene expression and maturation evaluation of sheep oocytes cultured in medium supplemented with natural antioxidant source. S Afr J Anim Sci 48(2):261–270. https://doi.org/10.4314/sajas.v48i2.7

Basini G, Tamanini C (2000) Selenium stimulates estradiol production in bovine granulosa cells: possible involvement of nitric oxide. Domest Anim Endocrinol 18:1–17. https://doi.org/10.1016/s0739-7240(99)00059-4

Berry DP, Buckley F, Dillon P (2007) Body condition score andlive-weight effects on milk production in Irish Holstein-Friesiandairy cows. Animal 1:1351–1359. https://doi.org/10.1017/S1751731107000419

Bettina PM, Redgrove KA, McLaughlin EA, Nixon B (2017) Molecular mechanisms responsible for increased vulnerability of the ageing oocyte to oxidative damage. Oxid Med Cell Longe. https://doi.org/10.1155/2017/4015874

Bilodeau-Goeseels S, Kastelic JP (2003) Factors affecting embryo survival and strategies to reduce embryonic mortality in cattle. Can J Anim Sci 83(4):659–671. https://doi.org/10.4141/A03-029

Bindari YR, Shrestha S, Shrestha N, Tara Gaire N (2013) Effects of nutrition on reproduction- a review. Adv Appl Sci Res 4(1):421–429

Bosco D, Haefliger JA, Meda P (2011) Connexins: key mediators of endocrine function. Physiol Rev 91:1393–1445. https://doi.org/10.1152/physrev.00027.2010

Bridges GA, Kruse SG, Funnell B, Perry GA, Gunn PJ, Arias RP, Lake SL (2012) Changes in body condition on oocyte quality andembryo survival. Proc App Reprod Strat Beef Cattle:269–284

Brigelius-Flohé R, Maiorino M (2013) Glutathione peroxidases. Biochim Biophys Acta 1830:3289–3303. https://doi.org/10.1016/j.bbagen.2012.11.020

Britt JH (1992) Impacts of early postpartum metabolism on follicular development and fertility. Bov Proc 24:39–43. https://doi.org/10.21423/aabppro19916706

Budani MC, Tiboni GM (2020) Effects of supplementation with natural antioxidants on oocytes and preimplantation embryos. Antioxidants (Basel, Switzerland) 9(7):612. https://doi.org/10.3390/antiox9070612

Butler WR (2003) Energy balance relationships with follicular development, ovulation and fertility in postpartum dairy cows. Livestock Prod Sci 83:211–218. https://doi.org/10.1016/S0301-6226(03)00112-X

Cantoni O, Guidarelli A, Fiorani M (2017) Mitochondrial uptake and accumulation of vitamin C: what can we learn from cell culture studies? Antioxid Redox Signal. https://doi.org/10.1089/ars.2017.7253

Carenzi C, Verga M (2009) Animal welfare: review of the scientific concept and definition. Ital J Anim Sci 8(Suppl.1):21–30. https://doi.org/10.4081/ijas.2009.s1.21

Carlsson F, Frykblom P, Lagerkvist CJ (2007) Farm animal welfare – testing for market failure. J Agric Appl Econ 39(1):61–73. https://doi.org/10.1017/S1074070800022756

Castillo-Martín M, Bonet S, Morató R, Yeste M (2014) Comparative effects of addingβ mercaptoethanol or L-ascorbic acid to culture or vitrification-warming media on IVF porcine embryos. Reprod Fertil Dev 26:875–882. https://doi.org/10.1071/RD13116

Cebrian-Serrano A, Salvador I, Raga E, Dinnyes A, Silvestre MA (2013) Beneficial effect of melatonin on blastocyst in vitro production from heat-stressed bovine oocytes. Reprod Domest Anim 48:738–746. https://doi.org/10.1111/rda.12154

Ceko MJ, Hummitzsch K, Hatzirodos N, Bonner WM, Aitken JB, Russell DL, Lane M, Rodgers RJ, Harris HH (2015) X-Ray fluorescence imaging and other analyses identify selenium and GPX1 as important in female reproductive function. Metallomics 7:71–82. https://doi.org/10.1039/c4mt00228h

Chawalit S, Nguyen NT, Tseng JK, Lo NW, Tu CF, Ju JC (2012) Trichostatin A and ascorbic acid assist in the development of porcine handmade cloned embryos via different physiologic pathways. Reprod Sci 19:976–986. https://doi.org/10.1177/1933719112440049

Chen J, Guo Q, Pei YH, Ren QL, Chi L, Hu RK, Tan Y (2020) Effect of a short-term vitamin E supplementation on oxidative stress in infertile PCOS women under ovulation induction: a retrospective cohort study. BMC Womens Health 20(1):69. https://doi.org/10.1186/s12905-020-00930-w

Christenson LK (2010) MicroRNA control of ovarian function. Anim Reprod 7:129–133

D'Occhio MJ, Baruselli PS, Campanile G (2019) Influence of nutrition, body condition, and metabolic status on reproduction in female beef cattle: a review. Theriogenology 125:277–284. https://doi.org/10.1016/j.theriogenology.2018.11.010

da Silveira JC, Veeramachaneni DNR, Winger QA, Carnevale EM, Bouma GJ (2012) Cell-secreted vesicles in equine ovarian follicular fluid contain miRNAs and proteins: a possible new form of cell communication within the ovarian follicle. Biol Reprod. 86:71. https://doi.org/10.1095/biolreprod.111.093252

Dai X, Lu Y, Zhang M, Miao Y, Zhou C, Cui Z, Xiong B (2017) Melatonin improves the fertilization ability of post-ovulatory aged mouse oocytes by stabilizing ovastacin and Juno to promote sperm binding and fusion. Hum Reprod 32:598–606. https://doi.org/10.1093/humrep/dew362

De Bie J, Marei WFA, Maillo V, Jordaens L, Gutierrez-Adan A, Bols PEJ, Leroy JLMR (2017) Differential effects of high and low glucose concentrations during lipolysis-like conditions on bovine in vitro oocyte quality, metabolism and subsequent embryo development. Reprod Fertil Dev 29:2284–2300. https://doi.org/10.1071/RD16474

Desmet KL, Van Hoeck V, Gagné D, Fournier E, Thakur A, O'Doherty AM, Walsh CP, Sirard MA, Bols PE, Leroy JL (2016) Exposure of bovine oocytes and embryos to elevated non-esterified fatty acid concentrations: integration of epigenetic and transcriptomic signatures in resultant blastocysts. BMC Genomics 17(1):1004. https://doi.org/10.1186/s12864-016-3366-y

Diao YF, Oqani RK, Li XX, Lin T, Kang JW, Jin DI (2014) Changes in histone H3 lysine 36 methylation in porcine oocytes and preimplantation embryos. PLoS One 9(6):e100205. https://doi.org/10.1371/journal.pone.0100205

Eler JP, Silva JA, Ferraz JB, Dias F, Oliveira HN, Evans JL, Golden BL (2002) Genetic evaluation of the probability of pregnancy at 14 months for Nellore heifers. J Anim Sci 80:951–954. https://doi.org/10.2527/2002.804951x

Elis S, Desmarchais A, Maillard V, Uzbekova S, Monget P, Dupont J (2015) Cell proliferation and progesterone synthesis depend on lipid metabolism in bovine granulosa cells. Theriogenology 83(5):840–853. https://doi.org/10.1016/j.theriogenology.2014.11.019

Emori C, Sugiura K (2014) Role of oocyte-derived paracrine factors in follicular development. Anim Sci J 85(6):627–633. https://doi.org/10.1111/asj.12200

Farman M, Tripathi SK, Nandi S, Girish Kumar V (2015) Follicular fluid concentrations of metabolic stressors in normal, obese, metabolic stressed and emaciated ewes. Asian J Anim Sci 9:466–470. https://doi.org/10.3923/ajas.2015.466.470

Farman M, Tripathi SK, Tej NK, Nandi S, Gupta PSP, Mondal S, Venkatesh GK (2018) Metabolic stress indicators in ewes (Ovisaries) under post-parturient and high protein diet conditions. Asian J Anim Vet Adv 13:360–368. https://doi.org/10.3923/ajava.2018.360.368

Ferreira RM, Chiaratti MR, Macabelli CH, Rodrigues CA, Ferraz ML, Watanabe YF et al (2016) The infertility of repeat-breeder cows during summer is associated with decreased mitochondrial DNA and increased expression of mitochondrial and apoptotic genes in oocytes. Biol Reprod. 94:66. https://doi.org/10.1095/biolreprod.115.133017

Gao C, Han HB, Tian XZ, Tan DX, Wang L, Zhou GB, Zhu SE, Liu GS (2012) Melatonin promotes embryonic development and reduces reactive oxygen species in vitrified mouse 2-cell embryos. J Pineal Res 52:305–311. https://doi.org/10.1111/j.1600-079X.2011.00944.x

Gaviria SM, Morado SA, López Herrera A, Betancur GR, Álvarez RAU, Zuluaga JE, Cética PD (2019) Resveratrol supplementation promotes recovery of lower oxidative metabolism after vitrification and warming of in vitro-produced bovine embryos. Reprod Fertil Dev 31:521–528. https://doi.org/10.1071/RD18216

Gebremedhn S, Ali A, Gad A, Prochazka R, Tesfaye D (2020) Extracellular vesicles as mediators of environmental and metabolic stress coping mechanisms during mammalian follicular development. Front Vet Sci 7:602043. https://doi.org/10.3389/fvets.2020.602043

Gu L, Wang Q, Sun QY (2010) Histone modifications during mammalian oocyte maturation: dynamics, regulation and functions. Cell Cycle 9:1942–1950. https://doi.org/10.4161/cc.9.10.11599

Gunaretnam I, Pretheeban T, Rajamahendran R (2013) Effects of ammonia and urea in vitro on mRNA of candidate bovine endometrial genes. Anim Reprod Sci 141(1–2):42–51. https://doi.org/10.1016/j.anireprosci.2013.07.001

Hailay T, Hoelker M, Poirier M, Gebremedhn S, Rings F, Saeed-Zidane M et al (2019a) Extracellular vesicle-coupled miRNA profiles in follicular fluid of cows with divergent post-calving metabolic status. Sci Rep 9:12851. https://doi.org/10.1038/s41598-019-49029-9

Hailay T, Hoelker M, Poirier M et al (2019b) Extracellular vesicle-coupled miRNA profiles in follicular fluid of cows with divergent post-calving metabolic status. Sci Rep 9:12851. https://doi.org/10.1038/s41598-019-49029-9

Halama A, Riesen N, Möller G, Hrabě de Angelis M, Adamski J (2013) Identification of biomarkers for apoptosis in cancer cell lines using metabolomics: tools for individualized medicine. J Intern Med 274:425–439. https://doi.org/10.1111/joim.12117

Hancock RL, Dunne K, Walport LJ, Flashman E, Kawamura A (2015) Epigenetic regulationby histone demethylases in hypoxia. Epigenomics 7:791–781. https://doi.org/10.2217/epi.15.24

Hefnawy AEG, Tórtora-Pérez JL (2010) The importance of selenium and the effects of its deficiency in animal health. Small Ruminant Res 89:185–192. https://doi.org/10.1016/j.smallrumres.2009.12.042

Hemmings KE, Leese HJ, Picton HM (2012) Amino acid turnover by bovine oocytes provides an index of oocyte developmental competence *in vitro*. Biol Reprod 86:1–12. https://doi.org/10.1095/biolreprod.111.092585

Hemmings KE, Maruthini D, Vyjayanthi S, Hogg JE, Balen AH, Campbell BK, Leese HJ, Picton HM (2013) Amino acid turnover by human oocytes is influenced by gamete developmental competence, patient characteristics and gonadotrophin treatment. Hum Reprod 28(4):1031–1044. https://doi.org/10.1093/humrep/des458

Hirshfield AN (1991) Development of follicles in the mammalian ovary. Int Rev Cytol 124:43–101. https://doi.org/10.1016/s0074-7696(08)61524-7

Hoedemaker M, Prange D, Gundelach Y (2009) Body condition change ante- and postpartum, health and reproductive performance in German Holstein cows. Reprod Domest Anim 44:167–173. https://doi.org/10.1111/j.1439-0531.2007.00992.x

Hung WT, Hong X, Christenson LK, McGinnis LK (2015) Extracellular vesicles from bovine follicular fluid support cumulus expansion. Biol Reprod 93:117. https://doi.org/10.1095/biolreprod.115.132977

Ibtisham F, Zhang L, Xiao M, An L, Bilal M (2017) Genomic selection and its application in animal breeding. Thai J Vet Med 47:301–310

Ibtisham F, Nawab A, Li G, Xiao M, An L, Naseer G (2018) Effect of nutrition on reproductive efficiency of dairy animals. Medycynaweterynaryjna. https://doi.org/10.21521/mw.6025

Keerthikumar S, Chisanga D, Ariyaratne D, Al Saffar H, Anand S, Zhao K, Samuel M, Pathan M, Jois M, Chilamkurti N, Gangoda L, Mathivanan S (2016) ExoCarta: a web-based compendium of exosomal cargo. J Mol Biol 428(4):688–692. https://doi.org/10.1016/j.jmb.2015.09.019

Kowsar R, Marey MA, Shimizu T, Miyamoto A (2016) Urea induces T helper 2 (Th2) type environment at transcriptional level and prostaglandin E2 secretion in bovine oviduct epithelial cells in culture. J Dairy Sci 99:5844–5850. https://doi.org/10.3168/jds.2016-10874

Kowsar R, Iranshahi VN, Sadeghi N, Ahmad R, Miyamoto A (2018) Urea influences amino acid turnover in bovine cumulus-oocyte complexes, cumulus cells and denuded oocytes, and affects *in vitro* fertilization outcome. Sci Rep 8:12191. https://doi.org/10.1038/s41598-018-30774-2

Kubovicova E, Makarevic A, Stadnik L, Holasek R, Hegedusova Z (2013) Effect of body condition and season on the yield and quality ofcattle embryos. J Micro Biotechnol Food Sci 2(1):1426–1435

Kumar D, Gupta D, Shankar S, Srivastava RK (2015) Biomolecular characterization of exosomes released from cancer stem cells: possible implications for biomarker and treatment of cancer. Oncotarget 6:3280–3291. https://doi.org/10.18632/oncotarget.2462

Kwak SS, Cheong SA, Jeon Y, Lee E, Choi KC, Jeung EB, Hyun SH (2012) The effects of resveratrol on porcine oocyte in vitro maturation and subsequent embryonic development after

parthenogenetic activation and in vitro fertilization. Theriogenology 78:86–101. https://doi.org/10.1016/j.theriogenology.2012.01.024

Leroy JL, Vanholder T, Mateusen B, Christophe A, Opsomer G, de Kruif A, Genicot G, Van Soom A (2005) Non-esterified fatty acids in follicular fluid of dairy cows and their effect on developmental capacity of bovine oocytes in vitro. Reproduction 130:485–495. https://doi.org/10.1530/rep.1.00735

Leroy JL, Van Soom A, Opsomer G, Goovaerts IG, Bols PE (2008) Reduced fertility in high-yielding dairy cows: are the oocyte and embryo in danger? Part II. Mechanisms linking nutrition and reduced oocyte and embryo quality in high-yielding dairy cows. Reprod Domest Anim 43(5):623–632. https://doi.org/10.1111/j.1439-0531.2007.00961.x

Leroy JL, Valckx SD, Jordaens L, De Bie J, Desmet KL, Van Hoeck V, Britt JH, Marei WF, Bols PE (2015) Nutrition and maternal metabolic health in relation to oocyte and embryo quality: critical views on what we learned from the dairy cow model. Reprod Fertil Dev 27(4):693–703. https://doi.org/10.1071/RD14363

Lisboa LA, Andrade ER, Hertel MF, Melo-Sterza FA, Moreno K, Bracarense APFRL, Alfieri AA, Seneda MM (2009) Viability and growth of cattle preantral follicles after in vitro culture of ovarian fragments in α-tocopherol. Reprod Fertil Dev 22:318–319. https://doi.org/10.1071/RDv22n1Ab325

Lizarraga RM, Anchordoquy JM, Galarza EM, Farnetano NA, Carranza-Martin A, Furnus CC, Mattioli GA, Anchordoquy JP (2020) Sodium selenite improves in vitro maturation of Bosprimigeniustaurus oocytes. Biol Trace Elem Res. https://doi.org/10.1007/s12011-019-01966-2

Lu X, Wu Z, Wang M, Cheng W (2018) Effects of vitamin C on the outcome of in vitro fertilization-embryo transfer in endometriosis: a randomized controlled study. J Int Med Res 46(11):4624–4633. https://doi.org/10.1177/0300060518786918

Lucy MC (2019) Stress, strain, and pregnancy outcome in postpartum cows. Anim Reprod 16(3):455–464. https://doi.org/10.21451/1984-3143-AR2019-0063

Makki M, Saboori E, Sabbaghi MA, Aram R, Fallahian MH, Peyghambari F, Roustaei H, Ahmadi A (2012) Effects of selenium, calcium and calcium ionophore on human oocytes in vitro maturation in a chemically defined medium. Iran J Reprod Med 10(4):343–348. PMID: 25246896; PMCID: PMC4165952

Mallol A, Santaló J, Ibáñez E (2015) Improved development of somatic cell cloned mouse embryos by vitamin C and latrunculin A. PLoS One 10:e0120033

Mayada AE, Nadia AT,Abdel-Mohsen MH, Francois ARS (2015) Effect of antioxidant supplementation on in vitro maturation of Camelus Dromedaries oocytes. Nat Sci 13(2):17–24. http://www.sciencepub.net/nature

McDonough MA, Loenarz C, Chowdhury R, Clifton IJ, Schofield CJ (2010) Structural studies on human 2-oxoglutarate dependent oxygenases. Curr Opin Struct Biol 20(6):659–672. https://doi.org/10.1016/j.sbi.2010.08.006

Mehdi Y, Dufrasne I (2016) Selenium in cattle: a review. Molecules 21:545. https://doi.org/10.3390/molecules21040545

Miclea I, Pacală N, Hettig A, Zăhan M, Miclea V (2012) Alpha-tocopherol and ascorbic acid combinations influence the maturation of sheep oocytes. Sci Papers Anim Sci Biotechnol 45(1)

Mondou E, Dufort I, Gohin M, Fournier E, Sirard M-A (2012) Analysis of microRNAs and their precursors in bovine early embryonic development. Mol Hum Reprod 18:425–434. https://doi.org/10.1093/molehr/gas015

Morris CA (1980) A review of relationships between aspects of reproduction in beef heifers and their lifetime production. 2. Associations with relative calving date and with dystocia. Anim Breed Abstr 48:753–767

Nabenishi H, Ohta H, Nishimoto T, Morita T, Ashizawa K, Tsuzuki Y (2012) The effects of cysteine addition during *in vitro* maturation on the developmental competence, ROS, GSH and apoptosis level of bovine oocytes exposed to heat stress. Zygote 20(3):249–259. https://doi.org/10.1017/S0967199411000220

Nandi S, Shree USP, Kumar GV (2013) Metabolic stressors in ovine and caprine sera and ovarian follicular fluid. Appl Cell Biol 2:110–113

Nandi S, Mondal S, Pal DT, Gupta PSP (2015) Effect of ammonia-generating diet on ovine serum and follicular fluid ammonia and urea levels, serum oestrogen and progesterone concentrations and granulosa cell functions. J Anim Physiol Anim Nutr 100:309–331. https://doi.org/10.1111/jpn.12369. Epub 2015 Jul 27

Nandi S, Gupta PSP, Mondal S (2016) Ammonia concentrations in different size classes of ovarian follicles of sheep (*Ovisaries*): possible mechanisms of accumulation and its effect on oocyte and granulosa cell growth *in vitro*. Theriogenology 84(4):678–687. https://doi.org/10.1016/j.theriogenology.2015.10.007

Nandi S, Tripathi SK, Gupta PSP, Mondal S (2017) Effect of metabolic stressors on survival and growth of in vitro cultured ovine preantral follicles and enclosed oocytes. Theriogenology 104:80–86. https://doi.org/10.1016/j.theriogenology.2017.07.024

Nandi S, Tripathi SK, Gupta PSP, Mondal S (2018) Nutritional and metabolic stressors on ovine oocyte development and granulosa cell functions in vitro. Cell Stress Chaperones 23(3):357–371. https://doi.org/10.1007/s12192-017-0846-1

O'Callaghan D, Yaakub H, Hyttel P, Spicer LJ, Boland MP (2000) Effect of nutrition and superovulation on oocyte morphology, follicular fluid composition and systemic hormone concentrations in ewes. J Reprod Fertil 118:303–313

Ochiai A, Kuroda K, Ikemoto Y, Ozaki R, Nakagawa K, Nojiri S, Takeda S, Sugiyama R (2019) Influence of resveratrol supplementation on IVF-embryo transfer cycle outcomes. Reprod Biomed Online 39(2):205–210. https://doi.org/10.1016/j.rbmo.2019.03.205

Orisaka M, Tajima K, Tsang BK, Kotsuji F (2009) Oocyte-granulosa-theca cell interactions during preantral follicular development. J Ovarian Res 2(1):9. https://doi.org/10.1186/1757-2215-2-9

Pearson RA, Nengomasha E, Krecek RC (1997) The challenges in using donkeys for work in Africa. In: Meeting the challenges of animal traction. Proceedings of an ATNESA workshop. DebreZeit, Ethiopia, May 5–9, 1997, pp 190–198

Picco SJ, Anchordoquy JM, de Matos DG, Anchordoquy JP, Seoane A, Mattioli GA, Errecalde AL, Furnus CC (2010) Effect of increasing zinc sulphate concentration during in vitro maturation of bovine oocytes. Theriogenology 74(7):1141–1148. https://doi.org/10.1016/j.theriogenology.2010.05.015

Popescu S, Borda C, Lazar EA, Hegedüs CI (2009) Assessment of dairy cow welfare in farms from Transylvania. In: Proceeding of 4th Croatian & 4th international symposium on agriculture, pp 752–756

Prasad S, Tiwari M, Pandey AN, Shrivastav TG, Chaube SK (2016) Impact of stress on oocyte quality and reproductive outcome. J Biomed Sci 23:36. https://doi.org/10.1186/s12929-016-0253-4

Richani D (2014) Epidermal growth factor-like peptide signalling and oocyte in vitro maturation. PhD thesis, University of Adelaide

Roth Z (2017) Effect of heat stress on reproduction in dairy cows: insights into the cellular and molecular responses of the oocyte. Annu Rev Anim Biosci 5:151–170. https://doi.org/10.1146/annurev-animal-022516-022849

Roth Z, Hansen PJ (2005) Disruption of nuclear maturation and rearrangement of cytoskeletal elements in bovine oocytes exposed to heat shock during maturation. Reproduction 129:235–244. https://doi.org/10.1530/rep.1.00394

Rukkwamsuk T, Kruip TA, Wensing T (1999) Relationship between overfeeding and overconditioning in the dry period and the problems of high producing dairy cows during the postparturient period. Vet Q 21(3):71–77. https://doi.org/10.1080/01652176.1999.9694997

Sakatani M, Kobayashi S, Takahashi M (2004) Effects of heat shock on in vitro development and intracellular oxidative state of bovine preimplantation embryos. Mol Reprod Dev 67(1):77–82. https://doi.org/10.1002/mrd.20014

Santonocito M, Vento M, Guglielmino MR, Battaglia R, Wahlgren J, Ragusa M et al (2014) Molecular characterization of exosomes and their microRNA cargo in human follicular fluid:

bioinformatic analysis reveals that exosomal microRNAs control pathways involved in follicular maturation. Fertil Steril 102:1751–61.e1. https://doi.org/10.1016/j.fertnstert.2014.08.005
Schwab CG, Bozak CK, Whitehouse NL (1992) Amino acid limitation and flow to duodenum at four stages of lactation. 1. Sequence of lysine and methionine limitation. J Dairy Sci 75:3486–3502
Sharma RK, Agarwal A (2004) Role of reactive oxygen species in gynecologic diseases. Reprod Med Biol 3(4):177–199. https://doi.org/10.1111/j.1447-0578.2004.00068.x
Sharma A, Baddela VS, Becker F, Dannenberger D, Viergutz T, Vanselow J (2019) Elevated free fatty acids affect bovine granulosa cell function: a molecular cue for compromised reproduction during negative energy balance. Endocrine Connect 8(5):493–505. https://doi.org/10.1530/EC-19-0011
Silva M, Melo SA (2015) Non-coding RNAs in exosomes: new players in cancer biology. Curr Genomics 16(5):295–303. https://doi.org/10.2174/1389202916666150707154719
Smith OB, Akinbamijo OO (2000) Micronutrients and reproduction in farm animals. Anim Reprod Sci 60–61:549–560. https://doi.org/10.1016/s0378-4320(00)00114-7
Smith OB, Somade B (1994) Nutrition reproduction interactions in farm animals. In: Proceedings of the international foundation seminar on animal reproduction. Niamey, Niger, 17–21, pp 1–31
Sordillo LM (2013) Selenium-dependent regulation of oxidative stress and immunity in periparturient dairy cattle. Vet Med Int 2013:154045. https://doi.org/10.1155/2013/154045
Spears JW, Weiss WP (2008) Role of antioxidants and trace elements in health and immunity of transition dairy cows. Vet J 176(1):70–76. https://doi.org/10.1016/j.tvjl.2007.12.015
Starkey P, Jaiyesimi-Njobe F, Hanekom D (1995) Animal traction in South Africa: overview of the key issues. In: Starkey P (ed) Animal traction in South Africa – empowering rural communities. Gauteng, Development Bank of Southern Africa. A DBSA-SANAT, pp 17–33
Stewart KR, Veselovska L, Kim J, Huang J, Saadeh H, Tomizawa S, Smallwood SA, Chen T, Kelsey G (2015) Dynamic changes in histone modifications precede de novo DNA methylation in oocytes. Genes Dev 29(23):2449–2462. https://doi.org/10.1101/gad.271353.115
Sutton-McDowall ML, Gilchrist RB, Thompson JG (2010) The pivotal role of glucose metabolism in determining oocyte developmental competence. Reproduction 139(4):685–695. https://doi.org/10.1530/REP-09-0345
Sutton-McDowall ML, Wu LL, Purdey M, Abell AD, Goldys EM, MacMillan KL, Thompson JG, Robker RL (2016) Nonesterified fatty acid-induced endoplasmic reticulum stress in cattle cumulus oocyte complexes alters cell metabolism and developmental competence. Biol Reprod. 94(1):23. https://doi.org/10.1095/biolreprod.115.131862
Taniguchi K, Taketani T, Lee LM, Kizuka F, Tamura I, Sugino N (2009) Melatonin protects granulosa cells for progesterone production as an antioxidant in human ovarian follicles. Biol Reprod. 81(1):378
Tareq KM, Akter QS, Khandoker MA, Tsujii H (2012) Selenium and vitamin E improve the in vitro maturation, fertilization and culture to blastocyst of porcine oocytes. J Reprod Dev 58(6):621–628. https://doi.org/10.1262/jrd.2012-064
Tiboni GM, Bucciarelli T, Giampietro F, Sulpizio M, Di Ilio C (2004) Influence of cigarette smoking on vitamin E, vitamin A, beta-carotene and lycopene concentrations in human preovulatory follicular fluid. Int J Immunopathol Pharm 17:389–393
Tripathi SK, Farman M, Nandi S, Girish Kumar V, PSP G (2016a) Oviductal and uterine fluid analytes as biomarkers of metabolic stress in ewes (Ovisaries). Small Rumin Res 144:225–228. https://doi.org/10.1016/j.smallrumres.2016.09.022
Tripathi SK, Farman M, Nandi S, Mondal S, Gupta P, Kumar VG (2016b) In vitro culture of oocytes and granulosa cells collected from normal, obese, emaciated and metabolically stressed ewes. Anim Reprod Sci 170:83–89. https://doi.org/10.1016/j.anireprosci.2016.04.007
Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO (2007a) Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol 9:654–659. https://doi.org/10.1038/ncb1596

Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO (2007b) Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol 9(6):654–659. https://doi.org/10.1038/ncb1596

Valckx SD, Van Hoeck V, Arias-Alvarez M, Maillo V, Lopez-Cardona AP, Gutierrez-Adan A, Berth M, Cortvrindt R, Bols PE, Leroy JL (2014) Elevated non-esterified fatty acid concentrations during in vitro murine follicle growth alter follicular physiology and reduce oocyte developmental competence. Fertil Steril 102:1769–1776 e1761. https://doi.org/10.1016/j.fertnstert.2014.08.01

Van Hoeck V, Sturmey RG, Bermejo-Alvarez P, Rizos D, Gutierrez-Adan A, Leese HJ, Bols PE, Leroy JL (2011) Elevated non-esterified fatty acid concentrations during bovine oocyte maturation compromise early embryo physiology. PLoS One 6(8):e23183

Van Hoeck V, Leroy JL, Arias Alvarez M, Rizos D, Gutierrez-Adan A, Schnorbusch K, Bols PE, Leese HJ, Sturmey RG (2013) Oocyte developmental failure in response to elevated nonesterified fatty acid concentrations: mechanistic insights. Reproduction 145(1):33–44. https://doi.org/10.1530/REP-12-0174

Van Hoeck V, Rizos D, Gutierrez-Adan A, Pintelon I, Jorssen E, Dufort I, Sirard MA, Verlaet A, Hermans N, Bols PE, Leroy JL (2015) Interaction between differential gene expression profile and phenotype in bovine blastocysts originating from oocytes exposed to elevated non-esterified fatty acid concentrations. Reprod Fertil Dev 27:372–384. https://doi.org/10.1071/RD13263

Walters AH, Bailey TL, Pearson RE, Gwazdauskas FC (2002) Parity-related changes in bovine follicle and oocyte populations, oocyte quality, and hormones to 90 days postpartum. J Dairy Sci 85:824–832. https://doi.org/10.3168/jds.S0022-0302(02)74142-8

Wang F, Tian X, Zhang L, He C, Ji P, Li Y, Tan D, Liu G (2014) Beneficial effect of resveratrol on bovine oocyte maturation and subsequent embryonic development after in vitro fertilization. Fertil Steril 101(2):577–586. https://doi.org/10.1016/j.fertnstert.2013.10.041

Webb R, Garnsworthy PC, Gong JG, Armstrong DG (2004) Control of follicular growth: local interactions and nutritional influences. J Anim Sci 82(E-Suppl):E63–E74. https://doi.org/10.2527/2004.8213_supplE63x

Wilkanowska A, Kokoszyn'ski D (2015) Effect of diet and physical activity of farm animals on their health and reproductive performance. In: Handbook of fertility. https://doi.org/10.1016/B978-0-12-800872-0.00014-7

Wong SL, Wu LL, Robker RL, Thompson JG, McDowall ML (2015) Hyperglycaemia and lipid differentially impair mouse oocyte developmental competence. Reprod Fertil Dev 27(4):583–592. https://doi.org/10.1071/RD14328

Xu Y, Nisenblat V, Lu C, Li R, Qiao J, Zhen X, Wang S (2018) Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. Reprod Biol Endocrinol 16:29

Yamaguchi S et al (2012) Tet1 controls meiosis by regulating meiotic gene expression. Nature 492:443–447. https://doi.org/10.1038/nature11709

Yáñez-Mó M, Siljander PRM, Andreu Z, BedinaZavec A, Borràs FE, Buzas EI et al (2015) Biological properties of extracellular vesicles and their physiological functions. J Extracell Vesicles 4:27066. https://doi.org/10.3402/jev.v4.27066

Yenuganti VR, Viergutz T, Vanselow J (2016) Oleic acid induces specific alterations in the morphology, gene expression and steroid hormone production of cultured bovine granulosa cells. Gen Comp Endocrinol 232:134–144. https://doi.org/10.1016/j.ygcen.2016.04.020

Young JI, Züchner S, Wang G (2015) Regulation of the epigenome by vitamin C. Annu Rev Nutr 35:545–564. https://doi.org/10.1146/annurev-nutr-071714-034228

Yu XX, Liu YH, Liu XM, Wang PC, Liu S, Miao JK, Du ZQ, Yang CX (2018) Ascorbic acid induces global epigenetic reprogramming to promote meiotic maturation and developmental competence of porcine oocytes. Sci Rep 8(1):6132. https://doi.org/10.1038/s41598-018-24395-y