

Review Article

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## Recent Strategies to Enhance Fertility in Farm Animals: An Overview

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### ABSTRACT

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With constant growth in livestock production, the falling fertility is emerging as cosmopolitan challenge to stakeholders nowadays. The high yielder modern dairy cows remain sub-fertile during lactation. Such detrimental effect on fertility needs to be apprehended by scientific community and practicing veterinarians under field. In this paper, we have reviewed some novel insights in the area of fertility enhancement by considering certain strategies. Further, this article also describes the various management, nutritional, prophylactic, therapeutic and breeding aspects to increase reproductive efficiency in farm animals.

### Introduction

Since last few decades, tremendous improvement in lactation yields have been achieved globally from dairy animals through various means. The commonest strategy to enhance milk yield have been remained genetic selection and thereby incorporation of high milk production genes in the low producing animals through genetic upgradation of existing stock. However, the animal researchers and scientists realized now that although milk yields have increased over the time, but the herd fertility rates of dairy animals have decreased simultaneously. The

high yielder modern dairy cows remain sub-fertile during lactation. However, in addition to milk production, other factors are likely to decrease reproductive efficiency in these herds (Bragança and Zangirolamo, 2018).

This undesirable consequence of falling fertility rates has become a great concern for dairy farmers which needs to be addressed immediately by veterinary fraternity with setting the objectives to characterize physiological periods limiting fertility performance and to define integrated management strategies for enhancing conception rates.

The condition can be managed by considering following key areas for improvement of the fertility *viz.*

Record keeping and logical analysis of huge data with special context to herd fertility indices

Reforming the breeding policies of genetic selection with emphasis on fertility biomarkers

Nutritional management of transition cows

Prophylactic management of reproductive disorders during peripartum period

Prevention and Control of Infectious Diseases and Parasitic infestations through regular Vaccination and Deworming

Controlled Breeding Programmes through estrous/ ovulation synchronization

Prompt diagnosis of reproductive status through ultrasonography

Management of male fertility through cent percent AI coverage with proven semen

Metabolome and reproduction

### **Record keeping and logical analysis of huge data with special context to herd fertility indices**

An accurate and consistent assessment of the fertility status of a dairy farm is very crucial part of a control program (Noakes *et al.*, 2009). Record keeping has a vital role in factual evaluation and proper management of any livestock business. There is a significant effect of reproductive efficiency on dairy economy. For evaluation of the fertility status of a farm, quantification of certain reproductive values is an essential prerequisite and to do same, it is obligatory to have access to reproductive records. One has to maintain the record of every cow regarding the reproductive parameters like Age at puberty, Age at first calving, Submission rate, Calving interval, Service period, Days open, Artificial insemination, Conception rate, Overall calving rate etc. Computer-based

systems now allow regular and almost constant review of a herd's fertility parameters. Herd data thus produced can be analyzed and compared with the standards and target levels so as to understand the lacunae and critical control points. To improve the fertility, first of all, livestock owners have to realize the infertility and even subfertility conditions. One calf per year is the set target for the cow in order to get optimum benefits from the dairy business. This target can be achieved only if the cow gets conceived within 3 months of parturition and if she fails, then obviously external interference is required to make it pregnant through proper treatment.

In the meantime, internet and information technology has emerged and integrated in herd fertility management to gear up the understanding of cow records. In the recent past, many softwares (Cattle Max, NAVFARM, EasyFarm etc.) for dairy herd management have been evolved as computer assisted key management tools to supervise the reproductive health. Data recording and storage technologies are being developing at a rapid pace (Crowe *et al.*, 2018).

Innovative analytical tools are available in the market which can detect various metabolites in milk to predict reproductive performance. Mid-infra-red (MIR) spectrum of milk assessment system is now easily available for milk composition traits such as milk fat, protein and fatty acids (Gengler *et al.*, 2013). Latest diagnostic tools with inbuilt biosensors can provide wide range of information regarding genomics, proteomics, hormonal levels and fertility. Health biomarkers such as progesterone, L-lactate dehydrogenase (udder health), urea and  $\beta$ -hydroxy butyrate indicate health status through analyzing the multitude of parameters in blood, milk and fecal samples from dairy cows (Friggens *et al.*, 2005, 2007; Egger-Danner *et al.*, 2015).

Composition of milk including somatic cell counts, temperature and color is detectable nowadays with help of inline sensors (Viguiet *et al.*, 2009; Hovinen *et al.*, 2011). Modern weighing machines and 3D cameras are recording the animal's body weight and body condition score while milking (Friggens *et al.*, 2004; Bewley *et al.*, 2008; Halachmi *et al.*, 2008; Weber *et al.*, 2014). Moreover, with the advent of sensor technology, dairy animals have been equipped with scratch cards (e.g., Estrotec; Rockway Inc., Spring Valley, WI), colour ampoules (Kamar Products Inc., Zionsville, IN), vasectomized bulls fitted with a chin-ball marker, the use of tail-painting methods or the electronic device HeatWatch, Collar sensors, Vocalization, Odor, pedometers and accelerometers that capture the animal's activities to predict specific behavior such as estrus and ill-health in dairy cows (Bewley *et al.*, 2010; Chapinal *et al.*, 2010). The quantum or format of the data is not a major constraint anymore; hence the use of such technologies and management systems will definitely add in the fertility and increase the overall production.

### **Reforming the breeding policies of genetic selection with emphasis on fertility biomarkers**

A major challenge for breeding programmes in terms of incorporation of fertility traits has been to develop phenotypes that have low heritability estimates. A second major issue for many fertility traits is to have easily measured phenotypic traits or genomic markers (single-nucleotide polymorphisms; SNPs) that correlate to appropriate fertility traits (Crowe *et al.*, 2018).

Discovery and development of biomarkers for prediction of uterine health and future fertility of heifers has paved new insights in the field of fertility augmentation. Milk based glycan markers have also been developed that can

predictively identify cows having retained placental membranes (Santoro *et al.*, 2016). Kekan *et al.*, (2019) evaluated the serum concentration of anti-mullerian hormone in heifers and anestrus Murrah Buffaloes and suggested that 200 pg/ml AMH concentration may be considered as cut-off value as a fertility marker. Such biomarkers that are easily measured in milk would allow animal breeders to select the cows with a propensity for improved uterine health and therefore move towards cows that would have increased fertility.

Reproductive function is supposed to decline when inbreeding percentage in a population exceeds by 6.25% (Hansen *et al.*, 2005) due to increased frequency of identical alleles at a gene locus. Crossbreeding is the best policy to avoid inbreeding depression, but nowadays conservation of indigenous breeds is the demand of moment and hence under these circumstances, use of AI with semen of different sires of the same breed from distant geographical location may be an alternative to minimize the inbreeding coefficient.

While in-vitro fertilisation (IVF) and embryo transfer are now significant tools to increase genetic selection on the female side with *Bos indicus* cattle (Morotti *et al.*, 2014), currently multiple ovulation and embryo transfer remains the more cost-effective method for *Bos Taurus* cattle (Holstein-Friesian, Brown Swiss, Jersey etc.) at population level. This is because the *Bos Taurus* breeds only produce between 5 to 20 follicles per follicle wave emergence event (Forde *et al.*, 2011), which is insufficient numbers of ova for effective culture for IVF.

Semen production centers must be covered under Govt. regulations to not supply semen in the same local area for use. Simultaneously, field veterinary officers and AI workers must be bound under strict rules

to use the semen produced at semen labs located outside of the local radius on rotation basis. Such policies will help to minimize the descent of identical genes in an individual and thereby will reduce infertility due to inbreeding depression.

Additionally, Govt. should encourage the research projects emphasizing on animal genetics and breeding targeted to study of correlation (both positive and negative) between production genes and fertility genes and thereby selection of positively correlated genes while exclusion negatively correlated genes of production and fertility in breeding programmes.

### **Nutritional management of transition cows**

Transition period is the duration consisting of three weeks before and three weeks after parturition. The transition period, although short, is the phase during the productive cycle of lactating cows when most metabolic and infectious diseases occur, such as mastitis and metritis in the weeks immediately after birth, with implications for reproduction (Roche *et al.*, 2013). The rapid increase in fetal demands and the development of the mammary gland, including the initiation of the synthesis of milk constituents, causes major adaptive changes (physiological, metabolic and nutritional) characterizing the final period of gestation and the beginning of lactation. These changes reduce dry matter intake that leads to the mobilization of body stores of adipocytes. Most cows can cope up with this metabolic load (the total energy burden imposed by the synthesis and secretion of milk, which may be met by mobilization of body reserves). Metabolic stress however is defined as the amount of metabolic load that cannot be sustained by this mobilization, leading to the down-regulation of some energetic processes, including those that maintain general health. Hence, the over-mobilization of body stores

during the period of NEB (Negative Energy Balance) is a key factor for disease susceptibility in modern dairy cattle (Crowe *et al.*, 2018). Researchers have reported that the immune system of cows under metabolic stress is further reduced, demonstrating a relationship between metabolic status and peripartum immune function (Crookenden *et al.*, 2017).

Dairy cows are highly prone to NEB if not met with sufficient nutritional requirements during peak lactation yield at around first 4-6 weeks post calving. Since, reproduction is not a vital function of the body and it occurs only when basic body demands are fulfilled. It has been reported that reduced dry matter intake after calving can cause negative energy balance and thereby prolong the service period (Franco, 2006). The chronic negative energy balance leads to drop in concentrations of plasma insulin, glucose, and insulin like growth factor-I while it increases the serum concentration of growth hormone and NEFAs (non-esterified fatty acids). These metabolic and endocrine changes adversely affect the HPG (hypothalamic-pituitary-gonadal) axis and result in postpartum infertility. Therefore, the NEB status reflects ultimately as decline in the fertility through delayed postpartum ovarian rebound. The occurrence of negative energy balance, high concentrations of fatty acids, b-hydroxybutyrate and triacylglycerol in the liver, coincide with the resumption of ovarian cyclicity, development of follicles that supply oocytes for fertilization, uterine involution and remodeling (Roche *et al.*, 2018). Thus, together, these processes and metabolic states can affect pre and post-ovulatory reproductive function (Luttgenau *et al.*, 2016). Furthermore, in addition to post calving energy balance, pre-calving loss in body condition also has significant consequences for metabolic status, milk composition and subsequent health and hence, it should be acknowledged.

Ovarian follicles contain insulin receptors and cows with lower peripheral insulin levels in the immediate postpartum period suffer from retarded postpartum ovarian resumption and normal cyclicity among others with a higher risk to suffer from cystic ovarian disease. Therefore, glucogenic diets have been advocated in the immediate postpartum period aiming to enhance the peripheral insulin concentrations and advance normal ovarian resumption. Various nutritional strategies to restore energy balance in order to improve fertility rate in dairy animals are being attempted.

### **Provision of bypass fat in the animal diet**

This may enhance transcription of genes that encode proteins essential to reproductive events (Mattos *et al.*, 2000). Further, dietary fats increase the circulating cholesterol level which is the precursor of progesterone and other steroidal hormones ( Grummer and Carroll, 1991). Supplementary fats in diet can boost reproductive function through restoring energy balance or through specific actions of particular fatty acid on cellular function. Altered uterine and ovarian function can be intervened through specific fatty acid precursors in the diet to affect the synthesis and secretion of steroid, eicosanoid and/ or prostaglandins. Recently, numerous in-vitro studies have shown that feeding of fish meal and soybean meal improves the pregnancy rate through inhibition of PGF<sub>2</sub> $\alpha$  in the endometrial cell culture. Bovine somatotropin (bST) increases embryo development and embryo survival when coupled with a timed-insemination program or cows detected in estrus. Presence of a conceptus alters endometrial expression of genes and proteins in response to bST and nutraceuticals (*i.e.* unsaturated fatty acids such as eicosapentaenoic and docosahexaenoic acid in by-pass lipids) to improve pregnancy rates (Thatcher *et al.*, 2006).

### **Supplementation of antioxidants rich diet and herb**

There is burgeoning literature on the involvement of oxidative stress in the pathophysiology of infertility, assisted fertility and female reproduction. Oxidative stress plays many important roles in various physiological processes from oocyte maturation to the process of fertilization and also in embryonic development. Recently, scientific reports are published which indicate role of oxidative stress in the development of various infertility conditions in animals including buffalo. The pathological effects of oxidative stress are mediated through various mechanisms including lipid damage, inhibition of protein synthesis, and depletion of ATP (Kumawat, 2012).

Antioxidants are substances which interact with and stabilize free radicals and protect the cells through preventing the oxidation of cellular organelles by free radicals and thereby minimizing the damaging effects of reactive oxygen species and reactive nitrogen species. Nowadays, there is emerging enthusiasm in the use of antioxidants, either natural or synthetic in human medicine. A number of herbal formulations used in traditional Indian medicine are also some of the potent antioxidants which need to be explored in coming future. Use of antioxidants to improve the post thaw quality of semen has long been investigated.

Phytochemicals, plant based non-nutrient compounds are important components of the animal diet and have potential ability to function as antioxidants and also to regulate cell signaling pathways. The plant extracts and formulations with good antioxidant efficacy can be promising radioprotectors of the future. *Aegle marmelos* and *Murraya koenigii* plant leaves have been reported to be used as potential sources of natural

antioxidants (Kumawat, 2012). Treatment of cows with vitamin E and selenium can increase the rate of uterine involution in cows with metritis and improve fertilization rates in ewes and cows.

Enrichment of diet with extra vitamins and minerals is supposed to improve fertility as a “golden bullet” solution by various commercial companies manufacturing feed additives and supplements (Hurley and Doane, 1989).

### **Prophylactic management of reproductive disorders during peripartum period**

Resumption of ovarian activity with re-occurrence of normal estrous cycles and restoration of fertility are inversely proportional to incidence of peri-parturient metabolic and reproductive disorders. Marked negative changes in energy balance and reduced immuno-competence influence gonadotropic and metabolic hormones. Early recrudescence of ovarian activity was found to be associated with prompt uterine involution (Thatcher *et al.*, 2006). Post-partum health and reproductive performance were improved when by-pass lipids enriched in polyunsaturated fatty acids were fed in the pre- and post-partum periods.

Supplementation of Selenium and Vitamin E fortified mineral mixture in last month of gestation reduces the incidence of retention of fetal membranes. Calcium content of mineral mixture can prevent the chances of milk fever and other postpartum disorders associated to calcium metabolism. Likewise, feeding of herbal mild oxytocic preparations in last week of gestation will help in smooth calving and prompt dehiscence of placental membranes. Furthermore, these prophylactic dosages of minerals, vitamins and oxytocics in peripartum periods will maintain the uterine health and thereby speed up the rate of

involution as well as timely resumption of ovarian activity and postpartum fertility.

### **Prevention and Control of Infectious Diseases and Parasitic infestations through regular Vaccination and Deworming**

It is a well-established fact that infectious diseases either locally (uterus) or systemically have adverse effects on fertility directly or indirectly. Infectious diseases can affect the reproductive system in the following main ways:

Impaired sperm survival or transport in the female tract, leading to reduced rate of fertilization.

Direct effects upon the embryo - this includes infections that result in early embryonic death and those that infect the more advanced fetus or its placenta, resulting in abortion, stillbirths or the birth of weak calves.

Indirect effects upon embryo survival - this includes infections that have adverse effects upon uterine function and those that infect the maternal component of the placenta. Again, this result in embryonic death, fetal death with abortion, mummification or stillbirth.

Infections with pathogens like *Leptospira hardjo*, bovine viral diarrhoea or herpes viruses are known to reduce conception rates, while infections with *Neospora caninum* and emerging viruses like the bluetongue virus may cause foetal losses and abortions. Bovine herpes virus 4 is reported to have a tropism for endometrial cells and therefore should be specifically monitored and controlled in herds suffering from uterine diseases, particularly where other risk factors are controlled or ruled out (Donofrio *et al.*, 2007).

Hence, regular vaccination of infectious diseases should be followed round the year to

avoid incidence on farm as a gold standard i.e. “prevention is better than cure”.

Parasitic infestations also affect the fertility adversely through direct effect on reproductive system causing embryonic/fetal mortality, abortion and pyometra or indirect effects producing anemia and general debility. Therefore, routine deworming is advocated at farm half yearly after clinical diagnosis or fecal sample screening through EPG (Egg Per Gram).

### **Controlled breeding programmes through estrous/ ovulation synchronization**

Calving to conception interval when exceeds 3 months, it is likely to prolong calving interval and thereby contribute to the significant economic losses in dairy business. Pharmaceutical control of follicle, CL, and uterine function with PGF, GnRH and intravaginal progesterone releasing inserts, has permitted development of more optimal timed-insemination programs for first service. Postovulatory increases in progesterone may enhance pregnancy rates in targeted populations of lactating dairy cows, but timing and magnitude of the progesterone increases are pharmaceutically dependent.

Advent of controlled breeding protocols made it possible to induce estrus in postpartum anestrus animals with quiescent ovaries. Numerous hormonal protocols have been devised to induce follicular growth, luteolysis and ovulation with fixed time insemination (FTI) without the need for estrus observation. Fertility losses due to human error in estrus detection can be curtailed with use of such protocols and thus, it becomes a great strategic tool to improve conception rates and reproductive efficiency. Likewise, resynchronization of non-respondent cows coupled with the use of ultrasonography for early pregnancy diagnosis provides the

opportunity for a second timed-insemination within 3-5 days of a non-pregnant diagnosis (Thatcher *et al.*, 2006).

Basic approaches of estrous synchronization involve either shortening of luteal phase by PGF injections or extension of luteal phase using progesterone therapy. However, in both the methods, it is required to observe estrus signs intensively for breeding of respondent cases. The former approach includes two injections of prostaglandin  $F_{2\alpha}$  at 11 days apart, followed by AI of animals which are detected in estrus within next 4-5 days of second PGF injection. The limitation of this method is that it works in only animals having a functional CL or persistent CL, and hence, useful for estrus synchronization of cyclic animals, whereas estrus induction is not possible in true anestrus cases. However, the later approach is helpful for both the purposes, induction as well as synchronization of estrus. In this method, progesterone is administered (oral/ SC/ IM/ Intravaginal) for either a long period of 14-15 days (when used alone) or for a short period of 7-9 days (when used with PGF at  $P_4$  withdrawal).

Use of GnRH with basic synchronization methods facilitates ovulation synchronization and thereby provides opportunities for FTI in herds without significant investment of time and labour into estrus detection. The basic ovulation synchronization program is OvSynch protocol which involves Injection GnRH (@10  $\mu$ g on day 0),  $PGF_{2\alpha}$  (@ 500  $\mu$ g on day 7) and a second injection of GnRH (@10  $\mu$ g on day 9) followed by FTI at 17-24 hrs after second GnRH injection. However, first service conception rate to a single round of OvSynch is approximately only 30% and hence, various modifications have been made in basic OvSynch protocol to improve the pregnancy rate *viz.* preSynch, HeatSynch, doubleSynch, CoSynch, Estra-doubleSynch

etc. with variable success rate. Progesterone based programmes (7-8 days' protocol) using an intravaginal device incorporating GnRH at the start and PGF at the end (Day 7) gives better results in terms of synchronization and pregnancy rates in healthy cows.

### **Prompt diagnosis of reproductive status through ultrasonography**

Various methods are available to determine pregnancy status, these include return to oestrus, rectal palpation of the reproductive tract and ultrasound scanning to observe the reproductive tract.

In bovine reproduction, ultrasonography has become the utmost vital diagnostic tool for evaluating the female reproductive system. Ultrasound technology offers the assessment of pregnancy status and fetal viability early post breeding in order to identify animals that fail to conceive, improving reproductive efficiency, visualization of ovarian and uterine pathologies which are not accurately detected via rectal palpation, allowing appropriate therapies to be implemented. Using this technique, the diagnosis of pregnancy is usually determined from day 28 of pregnancy, and 30 days later it is usually performed to evaluate embryonic loss. A cow goes into anestrus if embryonic loss occurs after maternal recognition of pregnancy because CL becomes persistent. Prediction of impending embryonic/fetal mortality is possible through USG scanning. In case of ensuing embryonic mortality, the fetal fluid starts showing some haziness with echoic snowy reflections, which are indications of appearance of debris in the fluid due to disorganization of cellular contents of placental membranes. It is very essential to capture such non-pregnant animals at an earliest which are already inseminated, so that appropriate treatment can be instituted for inducing them into estrus and make them pregnant.

### **Management of male fertility through cent percent AI coverage with proven semen**

Even though, bull is considered as “Half of the Herd”, very less attention is paid on male side fertility. In most of the instances, female is blamed responsible for reproductive failures especially in Indian scenario, where natural service is dominant over artificial insemination at field level. . In a study examining the pregnancy outcome of 5883 inseminations, 1 of the 35 bulls that delivered semen was associated with a 2- to 2.5-fold increase in pregnancy rates [69]. The bulls routinely used for breeding in field condition are neither vaccinated, nor tested and proven, and hence carries high probability of being carrier of venereal diseases. Such bulls act as source of infection to whole herd covered by them. Sometimes, other reproductive disorders like testicular degeneration or seminal defects due to malnutrition or toxicity may be prevalent in stray bulls. Mating of female with such bulls always leads to conception failure and again chances of repeating the estrus in mated female are very less, as uterine infection sets on and cow develops metritis, pyometra and anestrus.

It is always recommended for artificial insemination to avoid reproductive failures due to male infertility. The semen straws produced at any semen station, are prepared from tested and proven bulls which are routinely vaccinated and screened for various diseases. Moreover, these bulls are maintained under scientific management systems and good plane of nutrition. Every batch of semen straws is tested for various fertility parameters like sperm concentration, mass motility, individual motility, post-thaw motility, Hypo-osmotic swelling test etc. However, infertility issues might be faced even with AI in few cases, due to semen quality deterioration as a result of mishandling of semen, in-expertise of AI technician, improper timing of AI, inaccuracy

in heat detection etc. which are entirely human caused errors.

Such errors can be abolished through critical control on semen handling by following the standard approaches of semen transport, timely refilling of cryocans with liquid nitrogen, semen thawing (37 °C, 30 Sec) and routine check-up of post-thaw motility. Skill development training programs can be organized periodically at Veterinary institutes for AI technicians. Farmers' training about heat signs, use of estrus detection aids and knowledge about proper timing of AI will be definitely helpful to enhance the fertility.

### **Metabolomes and reproduction**

Metabolomics is the study of the metabolome which comprises the myriad of low molecular weight metabolites (lipids, amino acids, vitamins) that influence cellular, tissue and organ function (Patti *et al.*, 2012; Dona *et al.*, 2014; Goldansaz *et al.*, 2017). Ovarian function in mammals is acutely sensitive to metabolic homeostasis, and the important role of the GH-IGF1 axis was established by various researchers. It is now emerging that the metabolome, both systemic and follicular, influences follicle growth, oocyte quality and embryo developmental competency (Collado-Fernandez *et al.*, 2012; Wallace *et al.*, 2012; Bertoldo *et al.*, 2013; Gerard *et al.*, 2015; Gu *et al.*, 2015; Krisher *et al.*, 2015). Follicular fluid provides a metabolomic micro-environment that supports oocyte growth and development (Dumesic *et al.*, 2015; El-Hayek and Clarke 2016; Guerreiro *et al.*, 2018). In a study that utilised abattoir cow ovaries, palmitic acid and total fatty acids were reduced, and linoleic acid increased, in follicular fluid of follicles that contained competent oocytes (Matoba *et al.*, 2014). Differences in follicular fluid concentrations of saturated fatty acids between Holstein-Friesian heifers and lactating cows were

associated with differences in fertility (Bender *et al.*, 2010). Lactating Holstein Friesian cows had different profiles of amino acids and fatty acids in follicular fluid compared with non-lactating cows and heifers (Forde *et al.*, 2016). Follicular fluid influences oocyte development through the cumulus layer (Zhang *et al.*, 1995) and the metabolome profile of cumulus undergoes changes during follicular growth in cattle (Uhde *et al.*, 2018).

Metabolomic analysis of spent culture media of IVF produced cattle embryos was able to distinguish between male and female embryos (Gomez *et al.*, 2016). The accuracy in predicting sex using spent culture media of bovine IVF embryos increased from early blastocysts (74%) to expanded blastocysts (86%) (Munoz *et al.*, 2014b). Metabolomics, proteomics and miRNA have also been applied to assess stage of embryo development and embryo quality (Rodgaard *et al.*, 2015). In a recent study, IVF and ICSI derived cattle embryos were associated with spent culture media with a different metabolomic signature (Li *et al.*, 2018). Dual assessment of the systemic metabolome of recipient cows, together with the metabolome of spent culture media, could predict the pregnancy outcome for transferred IVF embryos (Munoz *et al.*, 2014a) and conventional superovulated embryos (Munoz *et al.*, 2014c). These studies are providing new insight into the metabolite environment of ovarian follicles that is optimal for oocyte development and should lead to targeted nutritional strategies that enhance fertility in cattle (D'Occhio *et al.*, 2019)

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