RECENT ADVANCES IN OOCYTES *IN-VITRO* MATURATION PROCESS IN BOVINES

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ABSTRACT: Cattle play a vital role in national economy; therefore, the cattle population must be raised by all possible ways of production. Maturation of oocytes outside the body of animal is principal method in dairy production field which is used to produce the mature oocytes for pre-implantation embryo development. This technology has great potential to increase efficiency for both clinically and commercially purposes. In the last few decades, the progress in *in-vitro* Maturation (IVM) of oocytes has been very slow. Many factors affects the IVM of oocytes. However pre-IVM with cAMP modulators could contribute to the acquisition of developmental competence by bovine oocytes from small antral follicles through the modulation of EGF receptor signaling and oocyte-cumulus/cumulus-cumulus gap junctional communication, however, the main aim of the review is to understand the ability of oocyte development and its control mechanism during *in-vivo* and *in-vitro* processes. In addition, the various perspectives of *in-vitro* maturation of oocytes in bovines have also been discussed.

Keywords: *In-vitro* maturation, cattle, oocyte competency.

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IN-VITRO MATURATION

Modern reproductive technologies have been integrated with the latest genetic selection tools to improve economically important traits, including fertility. While reproductive technologies are designed to help with everyday farm-level management problems, genetic selection is aimed at increasing fertility on a long-term genetic basis (Fleming *et al*., 2018). Since many factors affect fertility traits, and the phenotypes currently collected are quite removed from the actual biology of the animals (e.g. non-return rate, interval from calving to first service), the accuracy of breeding values for fertility is generally low. Nevertheless, genome-wide association studies (GWASs) have been successfully applied to fertility-related traits and several quantitative trait loci (QTL) were detected (Khatib, 2014). In addition, functional genomic approaches have been applied to some traits such as early embryo development and conceptus–maternal interactions, which are important for a successful gestation, as well as for embryo quality (Jaton *et al*., 2017). This review provides a detailed understanding and recent developments related to one of modern reproductive technology called oocyte *in-vitro* maturation (IVM). The IVM is a propagative method used to produces the mature oocytes *in-vitro* in the absence of gonadotropins. The IVM procedure is composed of manual removal of cumulus-oocyte complexes (COCs) from antral follicles and their culturing them under cell culture circumstances until attainment of metaphase II. A minor fraction of these mature oocytes has sufficient progressive potential (Schroeder 1984; Kanwichai and Panasophonkul, 2019). The efficiency of oocyte IVM method depends on the developmental ability of oocyte. The biochemical and molecular state of oocyte helps in the maturation of oocyte for fertilization and maturation to an embryo. A developing embryo is capable of its development to delivery of fetus. One of the important tasks still in the field of reproduction and developmental biology is to understand the composition of progressive oocyte capacity, with the role of the ovarian follicular environment around the oocyte in its progression to overall developmental potential. Somatic cells of follicles, especially CC (CCs), perform a crucial role for oocyte maturation during *in vivo* conditions (Gilchrist *et al.,* 2007). Generally, the Oocytes are present within the female's body at the time of birth. The egg does not undergo maturation in the ovary until attainment of puberty, where, the hormonal changes cause the egg to mature and then release periodically (Santonocito, 2014). Oocytes are collected from ovaries before ovulation and allowed for maturation and fertilization using sperm (Zimmerman *et al*., 2011). A few years ago, some or all the eggs used for collection which could not able to fertilize because they were not mature, but now maturation is done in laboratories using IVM technique. Immature and mature embryos can be stored for future use or they can be used immediately, fertilized after maturation and placed in female uterus expecting to get pregnant (Lagutina *et al.*, 2007).

IVM works more efficiently with modern techniques: Recently most of the research invested in the optimization of the *In vitro* Fertilization (IVF) process reaches to a very efficient procedure to improve genomic standards. The consolidative steps of IVM, IVF with sexed sperm, culture in defined media, biopsies and cryopreservation must all work almost perfectly to make an efficient approach. Since many of these steps are technically complex and sensitive to operators or environment, it remains a challenge to make it commercially viable (Sirad, 2018). New approaches, often developed in human beings, such as morpho-kinetics and aneuploidy screening using genomic (Treff and Zimmerman 2017) or less invasive techniques as free DNA (Liu *et al.,* 2017), may become affordable in cattle and improve pregnancy rates in the field. Today, we can foresee the use of IVM for CRISPR-Cas-9 related technologies that will allow precise genome editing or even epigenome editing. Indeed, the capacity to access the embryo at the pronuclear stage is important to minimize mosaicism and improve success rates of genome editing (Yum *et al.*, 2018).

How IVM works: The immature bovine oocytes are released out from their follicles and are cultivated in regular maturation medium, following that oocytes attain the first meiotic division stage (Sirard and Coenen, 2006). The Oocytes maturation conditions greatly affect the development of the blastocyst phase which affects both the developing capability embryo as well as the epigenetic composition of the embryo (Amarnath *et al.*, 2007). Through IVM, oocytes undergo through a sequence of cytoplasmic changes prior to the resumption of nuclear maturation which affects competence of the resulting embryo (Ferreira *et al*., 2009). A great number of oocytes are present at the time of birth in ovaries of females which are ovulated throughout the lifetime of a female. Ovulation occurs only when a female attains puberty, and it is stopped during pregnancy (Sirard and Coenen, 2006). This process is controlled by negative feedback of progesterone on LH, the interval of female's reproductive life is incomplete. In human females around 400 ovulations are recoded throughout the lifetime release (Macklon *et al.,* 2006). In cattle, reproductive life duration is much shorter, hence oocyte number present in ovary and number of ovulations also comparatively lower than human beings. For instance, in a dairy production system from each cow one calf is required in one year but the no of ovulation per year is very low as four to five. while it is considered that dairy cow ovulates a dominant follicle after 20 days of postpartum and get pregnant after an average 85 days and remains pregnant for nine months of pregnancy (Wiltbank *et al.*, 2014). In contrast, the male animal produces more than 10 billion sperm/ejaculate and can produce ten to thousands of offspring even after death due to cryopreservation of semen.

Oocyte maturation: For fruitful fertilization and embryo growth, the oocyte maturation is an essential event. Oocyte, in most mammals, entered into the initial phases of meiosis and stopped at prophase I during embryogenesis. The size of immature bovine oocyte is around 3 mm when it is enclosed by primordial (Palma *et al.,* 2012). Before restoring meiosis-I, the oocyte is 2n or 4C (*i.e.*, has four times the haploid pair of DNA) (Lonergan and Fair, 2016). After that, it arrests at the metaphase-II stage and follows by production of first polar body and oocyte has now DNA pair of 1n or 2C. After fertilization, there is a production of the second polar body, and embryo becomes diploid. Following attainment of 2n, the embryo divides mitotically and produces two identical daughter cells (Guevara, 2018) (Fig-1). *In-vivo*, meiotic resumption activity is controlled by a pre-ovulation surge in LH. Nevertheless, the elimination of meiotic arrest oocytes from can be restored using *in vitro* production methods for bovine embryos production (Combelles, 2013). In addition to the nuclear maturation, oocytes experience the cytoplasmic maturation, including rearrangement of many organelles, cortical granules, for fertilization process (Voronina *et al.*, 2003).

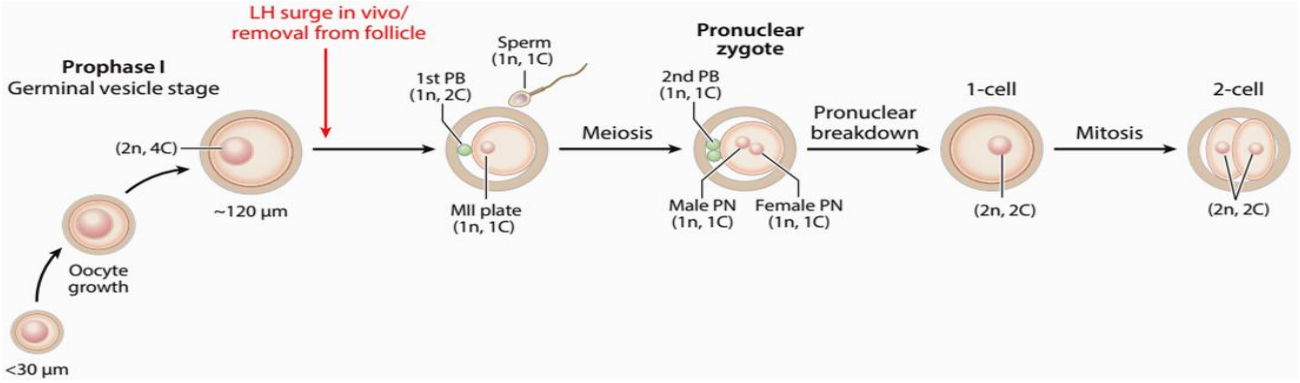

Figure 1. Stages of oocyte maturation during an improvement in the fetal ovary (adapted from Lonergan and Fair, 2016). PN: pronucleus

Significance: *In-vitro* maturation is a very useful method because it has the potential to collect a large number of oocytes from an ovary of dead or slaughtered animal. In livestock, the use of oocytes IVM to produce embryos from unstimulated ovaries is a routine practice and main technology for *in-vitro* embryo production, cloning and transgenic animal production. treatment of human sterility by IVM is not provided optimum results and not popular due to costs effects and side effects and less response of ovarian-stimulating hormones (Gilchrist *et al.,* 2007). However, mechanism of transfer of compounds between cumulus complexes and oocytes from gap junction in the last stage of follicular development has not been fully known (Smitz *et al.,* 2011). It is also not clear how the level of the transfer molecules affects the process of developing capacity. Hence, there is dire need to study the interaction between oocyte and their surrounding somatic cells during oocyte growth and maturation process (Combelles, 2013).

Oocytes recovery from the slaughtered animals

Preparations and precautions: Mammalian ovaries contain large quantities of immature oocytes which can be used for IVF and nuclear transfer to increase endangered and genetically superior animal population. In addition, these oocytes are also considered big and potential source of live offspring from female gametes which has not only for domestic and animal research use but also for various agricultural processes (Behbahanian *et al*., 2013). Amounts of material can be attained by collecting these ovaries from slaughter house and transporting them to laboratory whether in dry or in warm normal saline. From these collected ovaries, various immature and mature oocytes are achieved (Sirard *et al.,* 2006). For *in-vitro* production of good quality blastocysts, the culture media and oocyte collection procedure affect the oocyte developmental capacity (Gilchrist *et al.,* 2007). Collection of oocytes can be attained in four ways which include dissection the ovarian follicles (Thomas *et al.,* 2004), aspiration, slicing and rupturing the of visible surface of follicles (Wang *et al.,* 2007; Adona and Leal, 2004). Using the aspiration technique, the needle is used and the aspiration vacuum is important for collecting the good grade of oocytes. For each species, the needle gauge and aspiration pressure are determined like 18 gauge needle and 3 cm Hg vacuum provide good results to obtain the good quality oocytes in dairy cows (Wang *et al.,* 2007). The study has reported that slicing is a simple and actual way to collect high-quality buffalo oocytes from ovaries and recovery rate is about 5.7 oocytes per ovary (Rao *et al.,* 2010). Despite this, when using the slicing method, significantly minor oocytes were observed to reach the metaphase-II phase; this lower maturation rate might be due to additional pre-antral oocytes (Mehmood *et al.,* 2011). The previous studies show that recovery of oocytes by sectioning rather resulted in a significant rise in blastocyst production after IVM/IVF/IVC than aspiration. The collection of a sufficient number of oocytes is a pre-requisite for study of growth and optimization of fertility. Ovaries of the slaughtered animals are the inexpensive, easy access and prime source of oocytes for the process large scale by IVM and *in-vitro* fertilization (IVF) (Carolan *et al.,* 1993). On the other hand, most of slaughtered cattle and buffaloes are old, unfertile and/or unhealthy having reproductive disorders. Therefore, developing an effective oocyte collection process is very important for such animals. A primary goal of the oocyte recovery technique is to maximize the total number of oocytes and the produce of high-quality oocytes recovered from each ovary (evenly granulated cytoplasm enclosed by numerous layers of dense CC), which can be used for IVM, IVF, and *in-vitro* culture (IVC) processes (Behbahanian *et al*., 2013). Studied the effects of collection methods on the quantity and quality of oocytes improved per ovary, IVM, IVF, and subsequent embryonic development. Three techniques (slicing, puncture, aspiration I and II) were used. The results showed that the recovery of oocytes was higher when the slicing and puncture methods employed for oocyte collection compared to aspiration techniques. Different oocyte collection methods had no effect on nuclear maturation and subsequent embryo growing ability after IVF and IVC (Wang *et al.,* 2007).

Different phases of oocyte maturation: Oocyte maturation is a complex long-cell procedure containing meiotic cycle development (from diplotene to Metaphase-II) and reprogramming of cytoplasmic events, enabling oocytes to achieve their fertilization and embryogenesis (Eichenlaub *et al*.,2013). During follicular development, the oocytes grow, matured and acquire the ability to undergo fertilization and normal embryogenesis (Alm *et al*., 2017). *In vitro* mature oocytes would bypass the process of oocyte capacitation (superstructure modification occurs earlier than the LH peak, of the dominant follicular oocyte) (Ferreira *et al*., 2009), other considerable changes in the body under the influence of LH and follicular environment (Nardone *et al.,* 2010). These variations enable oocytes to achieve their full developing capacity which is divided into two classifications: one is the recovery and completion of the first meiosis, called nuclear maturation, and second is related to the functioning of cytoplasm, called maturation of cytoplasm (Chandrakant, 2010).

Nuclear Maturation: First time the meiotic maturation of mammalian oocytes was described in 1935 in rabbits (Coticchio *et al.,* 2013). In the following 60 years, many studies were carried out about the IVM of oocytes. The oocyte nuclear maturation defined as a sequence of nuclear modifications that occur during recovery and

progression of meiosis, resulting in haploid chromosome complements (Marteil *et al.,* 2009; Sirard *et al*., 2006). Generally, there are two involved steps: first, the oocyte has the ability to restart meiosis, go through germinal vesicles breakdown (GVBD) and increase to the metaphase-I; secondly, the oocyte has the ability to go beyond the metaphase-I, and enter the later stage into the metaphase-II. *In-vivo* oocytes recovered the occurrence of meiosis is due to preovulatory LH surge which is not seen *in-vitro* when oocytes removal from follicles happened (Grøndahl, 2008); (Sirard *et al*., 2006). When meiosis is restored in early stages, the oocytes possess the visible nuclei, called germinal vesicles (GV) and this GV undergoes a germinal vesicles breakdown (GVBD) (i.e., termination of the nuclear membrane) (Grøndahl, 2008). The nucleus quickly disappears after contact via the cytoplasm, and chromatin is reduced during the so-called diakinesis phase (Hashimoto *et al.*, 2019). During the movement, the nuclear membrane began to fold and the nuclear membrane disappeared. The formerly nuclear membrane fragments disappeared quickly while leaving only the double-walled small capsule (Tomek *et al.,* 2002). Afterward, the kinetochore reappears, the microtubules pull homologous genetic material and pair with meiotic spindles in the metaphase-I (M-I) (Grøndahl, 2008). This phase shows a significant reduction in mRNA transcription and a specific change in protein production (Tomek *et al*., 2006). Throughout *In vitro* maturation, RNA synthesis is strongly reduced because the compressed DNA present in the oocytes during GVBD stage which is actually ineffective for transcription, but translation only increases from GV to GVBD and reduce to the metaphase-II stage (Mahmoud and El-Naby, 2013); (Tomek *et al*., 2005). After the M-I stage, the oocytes must pass through the anaphase-I (*i.e.*, the chromosomes migrate to their relevant poles) and the Telophase-I (*i.e.*, the chromosomes establish on each pole are enclosed by the nuclear membrane). Oocytes are blocked in the metaphase-I are called "partially competent" for nuclear maturation (El-Raey and Nagai, 2014). When the metaphase II (M-II) occurs, the presence of the polar body (PB) can be identified, and the separation is completed. Now, the oocytes arrested at metaphase II until fertilization process (Grøndahl, 2008). Meiosis is resumed after fruitful fertilization which is confirmed by the presence of the second PB in oocyte (Table-1 and Fig-2) (El-Raey and Nagai, 2014).

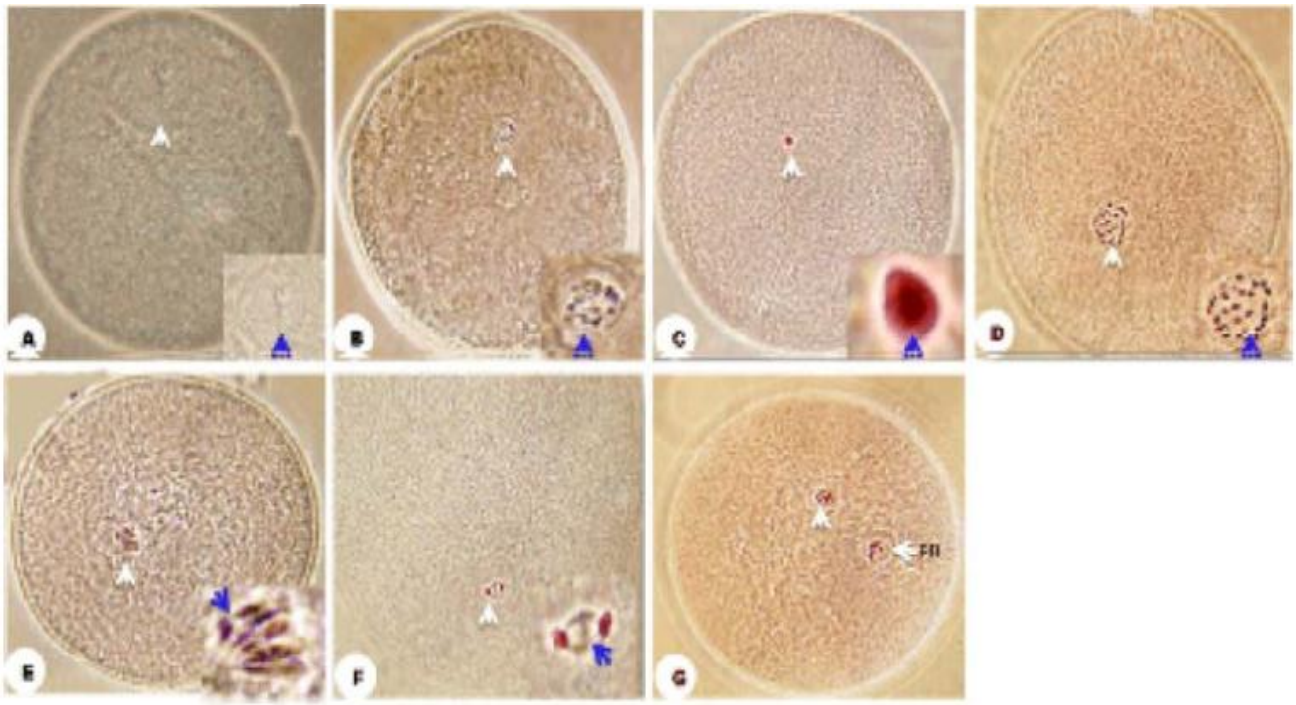

Figure-2: Stages of nuclear maturation of oocyte (A) GV (B) GVBD (C) Diakinesis (D) Metaphase-I (E) Anaphase-I (F) Telophase-I (G) Metaphase-II (adapted from (El-Raey and Nagai, 2014).

Table-1. Stages of nuclear maturation of oocyte (adapted from (El-Raey and Nagai, 2014)**.**

Stages	Definition
Prophase Leptotene	Chromosomes shrink
Zygotene	Synapse - homologous chromosome arrangement (bivalent); complex development of the association
Pachytene	Appearance of recombination nodes; shifting of genetic material
Diplotene	Cross formation, desynapsis; chromosome de coagulation and involvement in RNA synthesis
GV	large oocyte nucleus link between somatic cell called germinal vesicle
GVBD	Breakdown of Germinal vesicle breaks down of nuclear lamina and nuclear envelope
Diakinesis	Shortening of Chromosomes, tetravalent appearance, blockage of RNA production
Metaphase-I	on the metaphase plate of the spindle bivalents arrangement
Anaphase-I	Chromosomes move away from each other
Telophase-I	Progress of two daughter nuclei and production of the first polar body
Metaphase-II	Remaining chromatids quickly line up again on the second meiotic spindle

Cytoplasmic maturation: Cytoplasmic maturation of oocytes is differentiated as the union of metabolic, molecular and super-structural developments, altering the normal fertilization of oocyte cytoplasm and gaining developmental capacity (Combelles *et al*., 2002). It contains the synthesis of a wide range of oocyte-specific developmental regulatory proteins, the re-localization of cytoplasmic organelles and changes in the oocyte membrane transport system (Zheng, 2007; Krisher, 2004). In addition, after transcription alteration of mRNA, the protein translation and alteration of protein substrates and collection of nutrients for oocyte growth, and the ability of oocytes to promote embryo development are also observed during this phase (Leibfried-Rutledge *et al*., 2005; Nie *et al.,* 2013). Furthermore, the processes of superstructure modification of the Golgi complex, the gathering of ribosomes and the rise of lattice alike structure also observed (Antelman *et al.,* 2008). However, numerous other components are molecular and stimulating involved factors are also seen during cytoplasmic maturation (Chmurzynska, 2010). Cytoplasmic maturation is usually divided into three main processes: organelle redistribution of cytoskeletal dynamics and molecular maturation (Ferreira *et al*., 2009), which can be used circuitously and retrospectively to assess the normal fertilization, cleavage and blastocyst growth of mature oocytes. Failure to whole cytoplasmic maturation is involved in hindering the fertilization, embryonic gene activation, blastocyst formation, and even post-implantation development processes. Additionally, the cumulus cell expansion, 1 PB squeezing and increased perivitel space are also affected by failure of cytoplasmic maturation (Antelman *et al.,* 2008). In overall, nuclear maturation is only observed morphologically which are required for proper arrangement of sequence of IVM, and cytoplasmic maturation delivers clear evidence about the achievement of oocyte maturation (Hsu *et al.,* 2014). Eventually, the importance of cytoplasmic maturation plays a vital role in the enhancement of oocyte capacity (Belgrade, 2006).

Cytoplasmic maturation play a key role in male prokaryotic formation (cytoplasmic maturation can be determined by the occurrence of male pronuclear formation), meiotic cell cycle development, initiation pathways compulsory for genetic and epigenetic processes and pre-implantation embryo developing capacity (Oehninger, S. and Barroso, 2007); Trounson *et al.,* 2001). In addition, it provides the basis for implantation, start of pregnancy and normal fetal growth (Behbahanian *et al*., 2013) therefore, the cytoplasm of oocytes maturation has received more attention in mammalian research (Lucidi *et al.,* 2003).

CHARACTER OF THE CUMULUS CELLS IN OOCYTE MATURATION

Oocyte Selection for IVM: Maximum 40-50% of the zygotes unable to reach blastocyst phase due to decrease in oocyte development potential. Hence the competent oocyte selection is prime requirement. On the basis, morphological features, the bovine oocytes are selected and the presence of cumulus cells complex (COC) is necessary for maturation of the oocyte. These cells to communicate through gap junction. Moreover, the oocyte nearby cumulus cells (CC) have a role in nuclear maturation, cytoplasm maturation and even male pronuclear formation (Luvoni *et al.,* 2005). In mouse CC are not needed for oocyte fertilization. Granuloma cells differentiate into the CC, and they produce a factor which is involved in cytoplasmic and oocyte maturation, moreover, the secretory product of CC involved in oocyte development (Su *et al.,* 2009). Oocytes which are surrounded by CC are the best predictive criteria because these oocytes have high percentage to reach maturity and have high embryonic development (Mermillod *et al.,* 2008). At the time follicular atresia, the cumulus cell expends cresyl brilliant blue vital staining is used for a better selection of oocytes. However oocyte selection

depends not on only morphology, but some other factors may involve e.g. follicular size, the capacity of bovine oocyte derivative from different follicular size to undergo regular fertilization and early embryonic growth (Lonergan and Fair, 2016). Three groups (large, medium, and small) of follicles were noted in different studies, and large follicles have higher chances of embryonic development and blastocyst rate (Wang and Sun, 2006). It has been observed that follicles of 6.7 mm size having oocytes with numerous layers of CC and high percentage to develop into morula/blastocyst stage (Lonergan and Fair, 2016).

CHANCES TO IMPROVE OOCYTE COMPETENCE

Prior to oocytes release from Follicle: Capacity of an oocyte to differentiate into blastocyst referred to as oocyte competence. For cytoplasmic development, the pituitary gonadotropin and proper correspondence with nearby cumulus complex are necessary (Deutsch, 2015). Follicular source of oocyte controls, its developmental potential, and it creates the impression that once the oocyte is expelled from its follicle, its competence is stopped. Natural oocyte competence capability remained emphatically connected via the measure of the antral follicle from which it is collected (Steinberg, 2007), the phase of the follicular wave and the place of development (*in-vivo* vs *in-vitro*) (Shimizu *et al.*, 2008). It is conceivable to control follicular development and in this way influence competence capability of the emerging oocyte. The drifting period between hormonal incitement and ovarian emergence, just as the time interim between ovary accumulation and oocyte desire (Browder, 2012), has been accounted for fundamentally influence resulting in oocyte advancement. In the following examination, the best outcomes were gotten when animal received the 6 infusions of FSH with a 48-h drifting period; controlling LH 6 h before OPU brought about 80% of oocytes collection which improved the blastocyst development. A similar finding revealed that the ideal period among FSH release and follicle development was 54 ± 7 h that is required and ideal for a collection of good oocyte quality in ovarian-stimulated cows (González and de Jesús, 2009). During last five years data shows that the treatment of superovulation and follicle stimulating hormone type did not influence the duration of ovarian response and oocyte competence rates for *in vitro* fertilization (Ellison and Ellison, 2009).

After oocytes release from follicle: Two wide methodologies had been employed to improve oocyte competence ability following follicle retrieval. The first is to extend and enforce the efforts for putative development of development culture medium for oocytes. Most of research centers practicing the IVM of cow oocytes utilize a moderate and simple oocyte development protocol that has not changed over the 30 years. Tissue culture medium 199 is usually used to develop Cumulus-oocyte complexes in complex media enhanced protein source by egg white or serum in the presence of gonadotropin (FSH, LH) as well as development aspects (e.g., epidermal development factors). Maturation happens in 5% CO2 in the air (∼20% O_2) in a moistened environment for roughly 24 hours; and maturation depends on changing the media (Arat *et al.*, 2003). Although, the uncertain improvements in growth have been accounted for the modification of maturing media, the yield of blastocysts that increases 40–50 percentage. The second method is an attempt to replicate intra-follicular circumstances for the oocyte in which meiotic arrest is retained (Sarmiento, 2014). One main reason for slow growth of immature oocytes which are obtained from slaughtered animal ovaries is collection from small and medium size follicles which diverse variety of chemicals in follicular fluid. If selected follicles allow becoming dominant then it takes many days to ovulate. Conversely, the oocyte at metaphase II develop into a size of 15-20 mm. Hence, retrieved oocytes submitted to IVM, albeit able to do high rates of molecular development, had short time to experience common cytoplasmic development. Also, the *in vivo*–developed oocyte develops within the follicular fluid and it rises with LH surge; interestingly, *in-vitro*, oocytes develop the following expulsion from the negative (from an administrative point of view) follicular fluid pressure without the stimulus by the LH surge. The composition of the follicular fluid variations during period from LH surge to ovulation also important for oocyte maturations (Klumpp, 2004). Buffalo oocytes developed with follicular fluid within 20 hours after the LH release results in higher cleavage rates in IVF procedure and a greater number of blastocysts than those developed in 0-h BFF (O'Brien *et al.*, 2000). Improved maturation media could be capable to prompt protocols of oocyte maturation *in-vitro*. It is notable that reasonable variations happen in the oocyte for final development and development as the follicle increments from 1 to 15– 20 mm (Arat *et al.*, 2003). The oocytes that are aspirated from over stimulated follicles prior to the LH surge show changes in their nuclear and cytoplasmic morphology, which is recommended as a necessary condition to complete the entire competence.

This would not just show the last oocyte development (*i.e.*, the procedure happening from the LH surge to ovulation) is noteworthy yet in addition that the period prior to LH surge may be critical for the oocyte competence capability. Notwithstanding unlimited alterations of the IVM medium, there might be a natural process for blastocyst production feasibly during *in-vitro*. The maturation treatment of smaller follicles is important to enhance the development competence of oocytes present in bigger follicles *in-vivo* (Chandrakant, 2010).

As a major aspect of the methodology for the *In vitro* development of buffalo developing embryo, IVM is started quickly after the removal of the developing oocyte from small antral follicles because such oocytes may have neither the time nor the right condition to finish the important changes required for development of embryo. By eliminating the factors and resumption of meiosis, *in-vitro* utilizing meiotic inhibitors have been considered better choice for expression of mRNA or potentially protein collection in the oocyte for cytoplasmic maturation (Arat *et al.,* 2003). The commonest approach includes techniques that continued and upgraded the intra-oocyte dimensions of cAMP (counting cAMP analogs and adenylate cyclase activators, phosphodiesterase inhibitors) (Buell *et al.,* 2015) and it is also possible to prevent development by inhibiting protein binding or phosphorylation or by tracking cyclin-dependent kinases (Buell *et al.,* 2015). To prevent factors involved in hindering the meiotic resumption, proof for a beneficial outcome on oocyte capability should be assured by generating the data. Utilizing recent advances as pharmacological agents that permit synchronization of nuclear and cytoplasmic maturation of oocyte. The oocyte maturation period provides a connection emerging oocyte with cumulus for better fertility (Hodgen, 2012). The naturally the oocyte maturation is a general consideration and requirement for maturation and rearrangement of oocyte IVM during *in vitro* process subsequent fertilization and embryo production. The researcher has also observed role of cilostamide inclusion in maturation media for IVM and oocyte development for fertilization (Buell *et al.,* 2015). Additional modification of this or comparative cAMP-intervened pre-IVM culture frameworks could be possible to improve the productivity of IVM.

FACTORS AFFECTING ON *IN-VITRO* MATURATION

Oocyte related factors impacting on embryo quality: Embryo quality is extremely important for the development and support of successful pregnancy to full term. In cattle, most failed pregnancies result from embryonic mortality that occurs before implantation, during the first two weeks after fertilization (Lonergan and Fair, 2016). During this time, the fertilized oocyte undergoes profound morphological changes. In the oocytes, maternal RNAs and proteins are stocked, which during oogenesis sustains the first stages of development until embryonic genome activation. Inherited factors from the oocyte contribute to epigenetic re-programming and imprinting maintenance during early development (Lodde *et al*., 2017).

The *in vitro* maturation process may alter cumulus-oocyte crosstalk: In cattle, *in vitro* embryos are produced through successive steps which include IVM and IVF. The zygotes produced as a result undergo a seven day culture period that allows them to reach the blastocyst stage(Nuttinck, 2018). The morphological quality of embryo is assessed at the end of the culture period in order to select embryos that are compatible with the transfer procedure (Nuttinck, 2018). IVM implies that the cumulus-oocyte complex (COC) achieves its terminal differentiation in the absence of a follicular environment, and thus when luteinizing hormone induced granulosa cell cues are absent. While nuclear oocyte maturation appears to be progressing normally, other aspects of COC terminal differentiation may be altered. A comparison of CC transcriptomes obtained from *in vitro* matured COCs with those obtained from in vivo counterparts highlighted critical deficiencies affecting several cumulus molecular pathways known to support developmental potential of the oocyte in mice, humans and cattle (Brown *et al*., 2017). The expression of genes involved in several CC functions such as epidermal growth factor (EGF)-like signalling, extracellular matrix production, glucose metabolism, fatty acid metabolism and immune-like processes, were seen to be impaired during the *in vitro* procedure (Nuttinck, 2018). The alteration of terminal molecular events in CCs before fertilisation could compromise cumulus-oocyte dialogue and hence the full development of oocyte competence. Recent publications have recommended the supplementation of IVM media with bioactive molecules that are involved in cumulus-oocyte interplay in order to counterbalance the alterations induced by the *in vitro* procedure (Richani and Gilchrist 2018). It is reported that the addition of PGE2 to IVM/IVF media promotes embryonic cell survival and cell lineage development during the two weeks of the preimplantation period in cattle (Nuttinck *et al*., 2017). The CC support the stage IVM to MII of the oocyte and contribute in the cytoplasmic maturation required for optimal developmental capacities, such as male pronucleus formation and blastocyst stage development. The CC may be a good indicator of the meiotic ability of oocytes *in-vitro* (Davachi *et al.,* 2012). Oocyte granule cell gap junctions are essential for the synchronization of nuclear and cytoplasmic meiosis and are critical for oocyte maturation and successive embryonic development. In addition, physical interaction between oocytes and CC is considered essential for the transfer of nutrients and factors necessary for oocyte enlargement (Magnusson *et al.,* 2008). CC include preventing the zona pellucida from hardening, providing energy for oocyte maturation and production of cytoplasmic maturation factors, and nutrient uptake of oocytes during maturation in the medium. CC is also essential for fertilization. In addition, factors secreted by COCs (chemokines) induce sperm capacitation and enhance fertilization, providing evidence for a regulatory cycle between sperm and COCs during fertilization (Mori *et al.,*2000).

TCM -199 Medium And MEM: The culture medium, protein supplements, and hormones play a vital role in maturation and embryonic development for IVF. Different types of culture media are used that are TCM-199, minimum essential medium (MEM), Han's F-10 (Brad *et al.,* 2003; Rincón *et al.,* 2019). It has an edge over different mediums because of its composition. It contains essential amino acids and glutamine which stimulate DNA and RNA synthesis also enhance the cell division. It has a high concentration of glucose and glutamine which are poor energy substrates for CC. Hence TCM-199 is preferred over MEM (Kharche *et al.,* 2006).

Serum: Serum provides energy substrate amino acids and vitamins for maturation of embryo. Downs *et al*. (1986) suggested that it is beneficial to add serum because it protects zona pellucida from hardening because hardening adversely affects fertilization. Ravindranatha *et al.,* (2001) suggested that fetal calf serum improves the fertilization capacity of oocytes because it prevents the action of certain proteolytic enzymes, in turn, prevent hardening of zona pellucida. Also, serum has antioxidant property and it also balances the osmolarity. There are different sources for supplemented sera are estrus buffalo serum, steer serum, fetal calf serum and super-ovulated buffalo serum (Ravindranatha *et al.,* 2001).

Modulation of cyclic nucleotides during *in vitro* maturation: In mammalian oocytes, among the pharmacological approaches used for *in vitro* maturation to maintain meiotic arrest or at least to retard meiotic spontaneous resumption cAMP modulators are used. The aim to use cAMP modulators is to avoid premature nuclear maturation *in vitro* by means of maintaining higher concentration of cAMP within the ooplasm. This provides time for the COC to synchronize nuclear and cytoplasmic maturation, like that *in vivo* event that may result in more competent oocytes and embryo (Botigelli *et al*., 2017). Unsurprisingly, the mechanism of synthesis and hydrolysis of cGMP is one of the main targets of pharmacological strategies to control oocyte maturation. New approaches for modifying IVM and improve developmental competence take into consideration the knowledge from cGMP/cAMP and the use of dynamic systems.

New approaches in *in vitro* maturation and their impacts in the resulting embryo: Based on the significant advances of the mechanisms that control oocyte maturation and their interaction with the CCs, new paths were opened to improve the IVM technique. One of which is the use of dynamic *in vitro* systems to improve embryo quality and quantity, the so-called pre-maturation or pre-IVM systems (Botigelli *et al*., 2017). (Sugimura *et al*, 2018) reported that the administration of follicle-stimulating hormone (FSH) prior to oocyte retrieval improves oocyte developmental competence. During bovine embryo production *in vitro*, however, oocytes are typically derived from FSH-unprimed animals. In that study, the effect of pre-IVM with cAMP modulators (second messengers of FSH) was examined, on the developmental competence of oocytes derived from small antral follicles of FSH-unprimed animals. Pre-IVM with N6,2′-O-dibutyryladenosine 3′,5′-cyclic monophosphate (dbcAMP) and 3-isobutyl-1-methylxanthine (IBMX) for 2 h improved the blastocyst formation in oocytes stimulated by FSH or amphiregulin (AREG) (Sugimura *et al*, 2017). Furthermore, pre-IVM enhanced the expression of the FSH- or AREG-stimulated extracellular matrix-related genes and epidermal growth factor (EGF)-like peptide-related genes. These results indicate that pre-IVM with cAMP modulators could contribute to the acquisition of developmental competence by bovine oocytes from small antral follicles through the modulation of EGF receptor signaling and oocyte-cumulus/cumulus-cumulus gap junctional communication(Sugimura *et al*, 2018).

Conclusion: The different aspects which regulating oocyte developmental competence are continuously improving and these ideas change into progressive enhancements in oocyte IVM productivity. IVM is a complex process that depends on a number of aspects initiating from the recovery process and ending by its culture. It is the need of time to understand the above factors for efficient oocyte with high developmental competence. Furthermore, recent methods should be developed to get more insight into the oocyte developmental capability since the recovery of oocyte to the uterus for effective pregnancy rate after embryo transfer process.

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