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Review Article

Effects of Follicular Fluid Components on Oocyte Maturation and Embryo Development *In vivo* and *In vitro*

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Abstract | Oocytes of the antral follicles are bathed in extracellular fluid, which is termed follicular fluid (FF). Follicular fluid is synthesized from a transudate of blood plasma and from secretions of follicular cells. Oocytes in antral follicles persist in meiotic arrest until surge of luteinizing hormone and then start maturation. This suggests that follicular fluid before LH surge might contain meiosis inhibiting factor(s). Hence, inclusion of follicular fluid or cumulus cells or synthesized follicular component(s) during *in vitro* maturation of oocytes is expected to affect maturation of oocytes and development of the resulting embryos. Follicular fluid components might change during estrous cycle according to follicle size and/or animal nutrition. Concentration of follicular fluid components such as amino acids (AAs), meiosis activating sterol (FF-MAS), hyaluronan (HA), midkine (MK), carotenoids, antioxidants, urea, hormones and others is changed with follicles size and/or animal nutrition and effect on maturation of oocytes and development of the resulting embryos *in vivo* and/or *in vitro*. The present review article reviews and discusses these effects.

Keywords | Oocytes, Embryos, Maturation, Development, Follicular fluid, Nutrition

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INTRODUCTION

The duration of follicles' formation from primordial follicle stage to ovulation is differed among species (Hunter et al., 2004; van den Hurk and Santos, 2009). Follicular wave emergence is preceded by an increase offollicle stimulating hormone (Baby and Bartlewski, 2011). Granulosa cells around the time of follicular selection acquire LHreceptors that are essential for further development (Webb et al., 2003; Baird and Mitchell, 2013). Mature ovulatory follicles are characterized with high expression of aromatase in the granulosa cells, high concentration of estradiol hormone in follicular fluid and acquisition of LH receptors on granulosa cells (Shores and Hunter, 2003; Webb et al., 2003). Follicular diameter and follicular fluid composition are affected by follicular development and/or level of nutrition during estrous cycle (Mohammed 2011, Mohammed and Attaai 2011, Mohammed et al., 2012, Mohammed and Kassab 2015). This in turn affects oocyte maturation and subsequent embryo development. Some components are changed by follicular growth and development and/or by level of nutrition and are known to influence oocyte maturation and/or embryo development. Therefore, inclusion of follicular component(s) (Sinclair et al., 2008), follicular fluid (Mohammed et al., 2005; Spacek and Carnevale, 2018), cumulus cells (Mohammed 2006a,b; Mohammed 2008; Mohammed et al., 2008; Mohammed et al., 2010; Lee et al., 2018), supplements (Mohammed and Al-Suwaiegh, 2016; Mohammed 2017; Kassab et al., 2017; Mohammed and Al-Hozab 2018) during oocyte maturation *in vitro* or to live animals effects on maturation rate of oocytes and development of the resulting embryos. The present review article reviews and discusses these effects.

Follicular Fluid Effects

There are several studies (Mohammed et al., 2005; Madkour et al., 2016; Spacek and Carnevale, 2018) were carried to investigate the effect of follicular fluid supplementation to maturation medium on maturation rate and development of the resulting embryos. The results presented FF positive or negative effects of different species according to percentage of FF added, size of follicle, LH surge, animal feeding and animal species. In most studies, it is recommended to use; follicular fluid diluted (20-50%; Mohammed et al., 2005; Coelho Cruz et al., 2014), follicular fluid obtained from large follicle (Oberlender et al., 2013), follicular fluid obtained after LH surge (Kato and Seidel, 1998) during oocyte maturation *in vitro*. Such earlier conditions provide stimulatory effect on oocyte maturation and embryo development. In addition, Spacek and Carnevale (2018) studied the impact of equine and bovine oocyte maturation in follicular fluid from young and old mares on embryo production *in vitro***.** They concluded that FF from old mares has no deleterious impact on oocytes and their early developmental potential. Furthermore, Lee et al. (2018) studied the effect of co-culture canine cumulus and oviduct cells with porcine oocytes during maturation and subsequent embryo development of parthenotes *in vitro*. The obtained results demonstrated that co-culture with COC improved maturation of porcine oocyte and developmental competence of resulting embryo *in vitro*. Furthermore, such co-culture conditions enhanced the mRNA level of *SMAD2/3* and *GDF9*, and for embryo development by elevating the expression level of *PTGS2*, *WNT3A* and *MMP2*. In other study, Madkour et al. (2018) found that follicular fluid and supernatant from cultured cumulus-granulosa cells improve *in vitro* maturation in patients with polycystic ovarian syndrome.

Effects of Follicular Fluid Components

Some follicular fluid components were chosen in this section for presenting their effects on oocyte maturation and further embryonic development. They were chosen because they were used in several *in vitro* studies of mammalian oocytes. In addition, such follicular fluid components change over follicle development and/or nutrition.

Amino acids: Amino acids are components of follicular and tubal fluids required for oocytes'growth and maturation and embryo development (Guérin et al., 2012). Amino acids are uptake first by cumulus cells and transfer thereafter to the oocyte via gap junctions. There are several roles of amino acids in oocytes and the resulting embryos as protein synthesis, energy sources (Rieger et al., 1992), intracellular buffers (Bavister and McKiernan, 1993; Edwards et al., 1998), osmolytes (Dawson et al., 1998), heavy metal chelators (Bavister, 1995), and antioxidant compounds (Guérin et al., 2001). Amino acid composition of follicular fluid was used as predictors of *in vitro* embryo development. The amino acid composition of follicular fluid was associated with morphological quality of cumulus-oocyte complexes (COC) and with post-fertilization embryo development to the blastocyst stage (Sinclair et al., 2008). It has been found that inclusion of specific amino acids in culture media facilitates embryo hatching of embryos in some species (Liu et al., 1995; Pinyopummintr et al., 1996), helping to alleviate cultured-induced arrest.

Follicular fluid-meiosis activating sterol: Meiosis activating sterol (MAS) is found in the follicular fluid of several species and is termed follicular fluid–meiosis activating sterol (FF-MAS) (Byskov et al., 1995). Meiosis activating sterol was identified as intermediates in the cholesterol biosynthesis between landosterol and cholesterol (Rozman et al., 2002). Baltsen et al. (2001) found that equine follicular fluid concentration of FF-MAS increases with follicular size. Total FF-MAS concentration increases during follicular maturation and is significantly higher in dominant follicles compared to subordinate follicles. Luteinizing hormone was observed to be the key gonadotropin influencing FF-MAS activity in the rabbit ovary and providing evidence for the hypothesis that FF-MAS is part of ovarian physiology and plays a role in oocyte maturation *in vivo* (Grøndahl et al., 2003).

Follicular fluid–meiosis activating sterol is known to be an effective mediator in the resumption of meiosis (Byskov et al., 2002; Xie et al., 2004) and positively influences the survival rate of oocytes during *in vitro* maturation (Cavilla et al., 2001). A significant increase in the rate of oocytes reaching the metaphase II stage was observed after addition of 3 μM FF-MAS during oocyte maturation *in vitro* (86% in the treated oocytes versus 58% in untreated oocytes) (Donnay et al., 2004). However, the improvement observed in nuclear maturation did not lead to an increase in embryonic development after *in vitro* fertilization of calf oocyte. Furthermore, 20 μM FF-MAS improved nuclear maturation of human oocytes from patients suffering from polycystic ovarian syndrome (Grøndahl et al., 2000). Byskov et al. (2002) showed that MAS induces oocytes maturation *in vitro* even in oocytes depleted of cumulus cells. It also improves the cytoplasmic maturation of naked mouse oocytes by supporting the microtubules association and delaying the premature release of cortical granules (Hegele-Hartung et al., 1999). Cukurcam et al. (2003) concluded that FF-MAS induces full nuclear maturation to MII, and chromsomes segregate with high fidelity. FF-MAS appears to protect mammalian oocytes from precocious chromatid segregation. Surprisingly, Bergh et al. (2004) found that FF-MAS increased the rate of aneuploidy and had detrimental effects on cleavage and pre-embryo development, when exposed both before or after fertilization; this report needs further investigation. Smitz et al. (2007) investigating the safety of FF-MAS for *in vitro* maturation of hu-

man cumulus-enclosed oocytes. They found that inclusion of 1–10 μM FF-MAS in a 30-hour IVM protocol is safe. The effect of nutrition on FF-MAS concentration is not addressed and further investigation is still needed.

Hyaluronan (HA): Hyaluronic acid or hyaluronan is a major component of the extracellular matrix. Hyaluronan is the simplest glycosaminoglycan and plays several biological roles. In ovarian follicle, there are compact layers of cumulus cells surround the oocyte. They maintain intercellular communications with the oocyte and each other via an extensive network of gap junctions. An LH surge or hCG injection initiates a remarkable series of events, including synthesis and organization of hyaluronan into an extracellular matrix by the cumulus cells, and detachment of the expanded cumulus-oocyte complexes (COCs) from the follicle wall (Salustri et al., 1992). Some synthesized hyaluronan is released into follicular fluid and it has been demonstrated that HA delays death and prevents fragmentation of porcine oocytes (Sato et al., 1990 and 1994). The concentration of hyaluronan in FF containing an oocyte subsequently fertilized after insemination was significantly lower than that in FF containing an oocyte subsequently unfertilized. The concentration of hyaluronan in FF can be one of the indicators to estimate oocyte's viability of fertilization (Saito et al., 2000). Because HA was found in follicular fluid collected from follicles (2-8 mm) and before LH surge, further investigation are still needed to investigate HA concentration before and after LH surge.

When HA is added to the media of maturation and culture, it improves the developmental competence of bovine (Marquant-Le Guienne et al., 1999; Korosec et al., 2007) and porcine (Miyoshi et al., 1999) oocytes and embryos and their cells (Stojkovic et al., 1999). Stojkovic et al. (2002) found that blastocysts cultured in the presence of HA contained a similar total number of cells compared to *in vivo* derived embryos. There was an increase in the number of trophectoderm (TE) cells of embryos cultured with SOF-HA medium in comparison to embryos cultured in the presence of BSA, demonstrating that HA plays an important role in cell proliferation. In mice, increased rates of implantation and fetal development after blastocyst transfers were observed when HA was added to the culture medium (Gardner et al., 1999). Therefore, HA plays a positive role during *in vitro* culture of oocyte and embryo development and further embryonic development upon embryo transfer to recipient animals.

Midkine (MK): Midkine is considered the major heparin-binding growth factors in follicular fluid. The concentration of midkine in bovine follicular fluid is approximately 125 μg/l (Ohyama et al., 1994). Midkine is produced by granulosa cells under the control of gonadotropin hormones and might play a role in follicular growth (Karino et al., 1995). Minegishi et al. (1996) found also that the midkine mRNA level increased in a time- and dose- dependent manner in the presence of follicle stimulating hormone (FSH) in cultured granulosa cells of rat.

Addition of midkine during maturation of oocytes *in vitro* influenced their cytoplasmic maturation and increased blastocyst yields compared to untreated oocytes (Ikeda et al., 2000a; Ikeda et al., 2000b). The authors suggest that effects of midkine might be mainly mediated by granulosa cells. Furthermore, *in situ* hybridization studies have shown that midkine mRNA is restricted to the granulosa cells of healthy follicles of rats (Karino et al., 1995). Retinoic acid has been shown to induce a 2-fold increase in midkine mRNA at a concentration of 0.3 M (Minegishi et al., 1996). Treatment of bovine cumulus granulosa cells with 5 nM 9-*cis* retinoic acid similarly increased the expression of midkine mRNA (Royo et al., 2003). Therefore, vitamin A supplementation changes midkine concentration during oocyte growth development might be helpful for further embryonic development thereafter.

Carotenoids: Dietary carotenoids are thought to provide health benefits due to their role as antioxidants (Johnson 2002). Carotenoids in follicular fluid might serve as antioxidants and/or precursors of retinoid, which might modulate follicle, or oocyte functions. Mohan et al. (2003) conclude that cumulus cells contain endogenously active retinoid receptors and might be competent to synthesize retinoic acid using the retinol precursor. The same authors suggest that either retinoid administered *in vitro* or *in vivo* may have exerted a receptor-mediated effect on cumulus-granulosa cells. Further, administration of retinol *in vivo* and supplementation of retinoic acid during *in vitro* maturation results in enhanced embryonic development. Administration of retinol to cows in conjunctions with superovulation protocols increased the number of transferable blastocysts on day 7 (Shaw et al., 1995) and increased the yield of cumulus oocytes complexes from heifers following transvaginal ultrasound aspiration (Hidalgo et al., 2002).

Addition of 5nM 9-cis retinoic acid during pre-maturation of COCs in the presence of roscovitine improved cytoplasmic maturation and had a positive effect on blastocyst development and freeze-thaw survival rates (Duque et al., 2002). Embryos derived from cumulus oocyte complexes treated with 9-cis retinoic acid had higher total cell numbers than control ones. The same authors also provided evidence to show that 9-cis retinoic acid induced trophectoderm differentiation, altered inner cell mass to trophectoderm cell ratio and increased pregnancy rate following transfer of day 7 blastocysts (Hidalgo et al., 2003). These results gave evidence that retinol administration has potential effect on reproductive performance upon assisted reproductive techniques in mammals. Liang et al. (2012)

investigated the influence of 9-cis-retinoic acid on cytoplasmic and nuclear maturation and gene expression in canine oocytes during *in vitro* maturation. They found that inclusion of 5 nM 9-cis-RA was beneficial to nuclear and cytoplasmic maturation of canine oocytes during IVM. It is cleared that supplementing sources of carotenoids either in *vivo* or *in vitro*improves cytoplasmic and nuclear maturation of oocytes and further embryo development.

Antioxidant defenses: Reactive oxygen species (ROS) are produced in cells during normal aerobic metabolism. Several defense mechanisms against oxidative stress called antioxidant substances are present in both oocytes, embryos and their surroundings. Oocytes and embryos *in vivo* seem to be protected against oxidative stress by oxygen scavengers present in follicular and oviduct fluids. Duzguner et al. (2014) concluded that follicular fluid total antioxidant capacity seems to be a good predictor for estimating the quality of oocytes and embryos. Török et al. (2003) ascertained that the follicular fluid and endometrium samples contain active factors, which work as radical scavengers. Carbone et al. (2003) indicated that all the tested enzymes (catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase, glutathione transferase) were significantly expressed in human follicular fluid. Brad et al. (2003) found that glutathione content in mature porcine oocytes is correlated with subsequent fertilization and developmental success of embryos. They concluded that low intracellular glutathione might be in part responsible for lower developmental competence of embryos resulted from *in vitro* matured porcine oocytes. Dimitriadis et al. (2004) demonstrated that total antioxidant capacity (TAC) varies significantly between preovulatory bovine and ovine follicular fluid (Dimitriadis et al., 2004). Supplementing the maturation medium with IGF-1 + cysteamine improved the production of buffalo embryos significantly in *in vitro* culture (Singhal et al., 2009). In recent study (El-Shahata and Kandil, 2012), the concentrations of antioxidant enzymes antioxidants (glutathione, glutathione reductase and superoxide dismutase) vary according to the follicle size and the stage of the estrous cycle. We expect a possible role of antioxidant defense of follicular fluid in follicular growth and development due to increase metabolism. Consequently, supplementing follicular fluid to maturation medium of oocytes *in vitro*, which harvested from preovulatory follicles might enrich the medium with antioxidant capacity and improve developmental competence.

Urea: Diets of animals effect on follicular fluid composition and potential development of oocytes and embryos (Mohammed and Attaai, 2011; Mohammed et al., 2011; Valckx and Leroy, 2015; Mohammed, 2017).High levels of degradable protein and plasma ammonia concentrations increase the concentration of ammonia in bovine follicular fluid (Sinclair et al., 2000). High correlation was found between the concentration of urea in blood and follicular fluid in mares (Collins et al., 1997) and ewes (Mohammed et al., 2011). Studies of Leroy et al. (2004) and Mohammed et al. (2011) indicated that urea concentration decreased from small to large follicles in dairy cows and sheep, respectively. *In vivo*, dietary protein concentration influenced oocyte quality (Mohammed et al., 2011) with developmental competence negatively correlated with plasma urea levels (Armstrong et al., 2001). They hypothesized that nutrition induced changes in the ovarian IGF system may play a key role in regulating oocyte quality. McEvoy et al. (1997) found that embryos recovered from sheep with high levels of plasma urea were less viable compared with embryos recovered from sheep with normal level of urea. Dawuda et al. (2002) demonstrated a deleterious effect of excess dietary urea on the yield and quality of bovine embryos recovered 7 days after breeding. They only detected this effect if the period of urea feeding was initiated at the time of breeding and after the time of follicle selection. When feeding was started earlier, no harmful effect was noted on follicle selection, oocyte quality or on the yield and quality of embryos recovered 7 days after breeding. These data suggest that the cow is able to adapt within 10 days to the toxic effects of excess urea. Butler (2001) reported an inverse relationship between systemic urea and progesterone. He postulated that high dietary crude protein or systemic urea might impair fertility by interfering with the normal inductive effects of progesterone on the microenvironment of the uterus, leading to suboptimal conditions for the maintenance of embryo growth and development whereas (Kenny et al., 2002) found no evidence to suggest any reduction in plasma progesterone concentrations. Moreover, our study (Mohammed and Attaai, 2011) indicated that dietary urea level retarded delayed cleavages to four-cell stage embryos at the expected time.

Ammonia concentrations in fresh IVM control medium were low detectable (< 4μM) and increased to 13 μM at the end of the 24-h incubation period, indicating that a moderate amount of ammonia is generated from degradation of amino acids during the IVM period (Hammon et al., 2000a). DeWit et al. (2001) found that urea increased the rate of GVBD and development of metaphase I, but it impaired to some extent the transition from metaphase I to telophase I or metaphase II because urea is known to inhibit polymerization of tubulin into microtubules (Stoppin-Mellet et al., 1999). However, expression of embryonic development as percentage of the cleaved ones removed the negative effect of urea. This means that once the fertilized oocyte is cleaved, embryonic development is not apparently affected by exposure to urea. Exposure of bovine oocytes to ammonia concentration of 29-356 μM during IVM did not adversely influence embryo cleavage, morula or blastocyst development compared with the control ones (Hammon et al., 2000a). These results indicate that bo-

vine oocytes tolerated ammonia concentration similar to or even higher than those found in the early antral follicles. Hammon et al. (2000a and 2000b) indicated that the effect of ammonia on the preimplantation bovine embryos development depends on the concentration of ammonia, stage of development when exposure to ammonia occurs and the duration of exposure. Follicular fluid used diluted during IVM might lead to alleviate the concentration and deleterious effect of urea to a tolerable level for oocyte maturation and embryo development.

Leptin: Leptin receptors have been demonstrated in the granulosa and thecal ovarian cells. Leptin reduces steroid secretion by antagonizing IGF-I within these cells (Karlsson et al., 1997; Agarwal et al., 1999). Adipocytes are the major source of leptin synthesis and secretion. There are no published studies concerning changes in FF of leptin level during follicular growth and development. Regarding to the effect of nutrition on leptin level, Ferguson et al. (2003) found that leptin concentrations were consistently higher from day 3 of the estrous cycle in gilts receiving high feed intake, indicating that leptin concentrations are altering in response to feed intake rather than in response to changes in back fat depots. This is similar to finding of Blache et al. (2000) in sheep who found that leptin concentration elevated within 5 days after feed intake was increased. Huang et al., (2004) studied the impact of leptin levels on outcome over embryo transfer of *in vitro* produced embryos in women. They found that serum and follicular fluid leptin levels in successful pregnancies were significantly ($P < 0.05$) lower than that in women with failed conception suggesting leptin level in sera and follicular fluids at the time of oocyte retrieval might be predictive of IVF outcomes. Fedorcsák and Storeng (2003) were cultured two-cell stage mouse embryos in the presence of leptin; they found significantly fewer leptin-exposed than control embryos hatched by day 5 and 6 of development. Moreover, cells of leptin-exposed day 5 blastocysts showed a higher rate of DNA fragmentation, which is a sign of apoptosis. It could be indicated that high leptin levels may interfere with the developing dominant follicles and further embryo development. Because *in vitro* fertilization-embryo transfer studies found negative relationship between serum and follicular fluid leptin levels and successful pregnancies (Huang et al., 2004), we expect also that leptin will have a negative effect of oocyte maturation and its viability *in vivo* and *in vitro* and further studies are still required to proof this expectation. Llaneza-Suarez et al. (2014) assessed follicular fluid leptin level as outcome predictor in women undergoing *in vitro* fertilization–intracytoplasmic sperm injection (IVF-ICSI). They found that high follicular fluid leptin levels were associated with low live birth rate after IVF-ICSI of oocytes. Therefore, it is seemed that feed intake or nutrition altered leptin levels during estrous or menstrual cycle, which consequently has a negative effect of embryo development.

Growth hormone (Somatotrophin): Nutritional state modulates growth hormone levels (Bergan et al., 2015). Receptors of growth hormone have been found in ovarian cells. Growth hormone concentrations in follicular fluid were positively correlated with fertilization, cleavage rate and pre-implantation embryo morphology (Mendoza et al., 1999). In addition, growth hormone is known to enhance intrafollicular metabolic events required for oocyte maturation such as FSH-dependent estradiol production by granulosa cells (Lanzone et al., 1996), FSH and LH receptors formation in granulosa cells (Jia et al., 1986) or androgen production stimulation by theca cells (Apa et al., 1996). The effects of growth hormone on bovine oocyte maturation *in vitro* were studied. Izadyar et al. (1996) reported an acceleration of *in vitro* maturation of cumulus-enclosed oocytes, induction of cumulus expansion, and promotion of subsequent embryonic development. Other study (Izadyar et al., 1998) indicated enhanced migration of cortical granules and sperm aster formation. Iga et al. (1998) showed increase rate of nuclear maturation and blastocyst formation of bovine oocytes in the presence of growth hormone. Shimizu et al. (2008) found involvement of insulin and growth hormone (GH) during follicular development in the bovine ovary. They suggest that the increase in the expression of growth hormone receptor (GHR) may be a turning point for follicles to enter the ovulatory phase during final follicular development and that the insulin system may support the maturation of preovulatory follicles. Sá Filhoa et al. (2009) studied the effect of recombinant bovine somatotropin (bST) on follicular population and on *in vitro* buffalo embryo production. They found that bST treatment improves the follicular population, demonstrating its possible application in buffalo donors submitted to ovum pick-up programs. Moreover, investigated the involvement of growth hormone in equine oocyte maturation, receptor localization and steroid production by cumulus–oocyte complexes *in vitro*. They found that addition of equine growth hormone to maturation medium increased rates of cytoplasmic maturation and had an important role in equine oocyte maturation, perhaps mediated by the presence of equine growth hormone-receptor in ovarian follicles.

Oestradiol: Level of nutrition alters metabolism of oestradiol-17β in dairy cattle (Sangsritavong et al., 2002). In addition, oestradiol level rises as follicle increases in size to the preovulatory follicle (Gordon, 2003). The oestradiol was found in the highest concentration when bovine follicles reached ~15 mm in diameter (Short, 1962). The oestradiol concentration in follicular fluid obtained from follicles that contained oocytes, which were fertilized thereafter, was greater than that in follicles containing oocytes, which were not fertilized (Subramanian, 1988). Dode and

Graves (2003) investigated the role of oestradiol-17 beta on nuclear and cytoplasmic maturation of swine oocytes *in vitro*. The results suggest that oestradiol is not involved in maturation of swine oocytes. *In vitro* studies indicate that presence of oestradiol during maturation resulted in nuclear aberrations in bovine oocyte (Beker et al., 2002). Therefore, the role of oestradiol in oocyte maturation and embryo development *in vitro* is not clear.

CONCLUSION

Follicular fluid is a complex of serum restricted components and follicular-synthesized secretions. There are differences in follicular fluid compositions due to follicle size,level of nutrition and animal species, which either stimulate or inhibit oocyte maturation and further embryonic development.

CONFLICT OF INTEREST

There is no conflict of interest in this review to declare.

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AUTHORS' CONTRIBUTION

All persons who have made substantial contributions to the work reported in the manuscript.

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