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Role of Some Inducing Additives in in vitro Maturation Environment of Farm Animal's Oocytes: Status Evaluation

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Abstract. This review focused on highlighting the importance of the biochemical role of some additives that have a stimulating impact on in vitro maturation (IVM) of farm animal oocytes. The supportive role that these additives played has led to a noticeable increase in embryos yields. Nevertheless, there are some considerations that must be taken into account for the process of producing embryos in vitro to function optimally. Among the hormones, the famous gonadotropic hormones (follicle-stimulating hormone (FSH), luteinizing hormone (LH) and chorionic gonadotropin hormone (CG)), estradiol and growth hormone (GH) occupied a wide area in IVM, but the usage of these hormones still limited to specific concentrations as the increase in their concentrations did not give the desired effect. Due to the historical popularity and the primary role of cysteamine as an antioxidant agent, its usage has increased recently. However, this usage has also remained limited to specific concentrations, as are hormones. Besides, cysteamine was an important reason for obtaining high rates of embryos in the blastocyst stage. Conversely, there was a reservation in the use of follicular fluid (FF) and fetal calf serum (FCS). Although these two elements are rich in hormones, proteins, lipids and various growth factors, FF contains factors that inhibit the maturation of oocytes. Moreover, FCS has a negative role in the quality of resulted embryos because of the high levels of lipids (triglycerides).

Keywords. Cysteamine, Fetal calf serum, Follicular fluid, Hormones, Oocytes.

1. Introduction

Since the emergence of *in vitro* embryo production technology (IVEP) until the present day, there have been persistent efforts being made to develop this important technology that has vigorously entered the world of assisted reproductive technology (ART) to be in turn one of the basic technologies that underpin other technologies including the division, cloning, multiplication, sexing and merging early developing embryos (1,2,3,4,5). The conditions in which this important technology began to appear are described as conditions in which the tools and tactics were not sufficiently developed to accelerate the progress compared with the tremendous scientific progress in those methods and tools currently. However, with this great improvement, most studies indicated little yield of blastocyst embryo stages concerning the number of collected oocytes by different ways, maturation, fertilization and division as the ratio did not exceed 40% (6). Many common maturation media have been produced, these media differ from each other in the chemical composition and the targeted animal species like Tissue Culture Medium -199 (TCM-199), Ham's F10, Ham's F12 and Modified Eagle Medium with Earle's modified salts (MEME). It can be said that the process of IVM has largely exceeded the prevailing perception that assumed the usage of common media as basic and specific environment to reach a new perception represented in the use of complex and dispersed maturation

methods that include several stimulating compounds of varying proportions. Thus, this made maturation processes stabilize in a new phase completely different from the initial stage that prevailed in a relatively long period. Hormones are one of the most important additives in IVM, especially the gonadotropic hormones (FSH, LH and CG), as the supply of these additives during the period of maturation (24-27 hours) has led to a significant increase in the yield of embryos (7, 8,9,10,11,12). There has been a widespread trend in studies towards the embodiment of serum and FF in the IVM environment since they achieve strong integration of performance with common maturation media. Due to the structure and biochemical properties of both FCS and FF, these two agents have been widely used in cell culture. Most studies have recommended the use of specific concentrations in a manner that ensures optimal production of embryos. Cysteamine is one of the most famous agents that have a prominent role in resuscitating cells and reducing oxidative damage, as this agent has largely dominated the processes of IVM and cell culture due to its historical fame in medicine and the treatment of some cases. In its action, cysteamine resembles the action of antioxidant enzymes such as superoxide dismutase which eliminates oxygen (O_2). The IVM environment lacks antioxidants, and as a consequence, cysteamine had to be added to support the antioxidant resistance caused by reactive oxygen species (ROS) (9,13). In this review, the vital role and the actual reality of the inducing additives (hormones, FCS, FF and cysteamine) in the IVEP technology were highlighted in terms of usage, concentrations, advantages, and limitations.

2. Hormones

In the ovary, the hormonal regulation is considered the basis for natural fertilization and subsequent embryonic development, where the oocyte undergos a strict sequence of morphological and physiological transformations in the cytoplasm and nucleus during meiosis. On the level of ART, hormones constituted a revolution in the IVEP. Virtually, no research targeting oocytes maturation is free of hormones additives. Most of studies that used hormones according to specific levels indicated a significant increase in the yield of the resulting embryos. However, the use of these additives is still limited to achieving a high, acceptable and required increase in embryos yields. Perhaps the main reason for this is the system that determines the concentrations of these hormones within the body which mainly relates to the requirements of each stage of growth and development of the follicle and the oocyte until they complete their final maturity. In this regard, Ginther *et al*. (14) studied in detail the extent of heterogeneity in hormones concentrations (FSH, LH, Oestradiol and progesterone) and their temporal relationship to the growth and differentiation of dominant follicles in mares (Figure 1). Within the IVM scenario, hormones are added according to several fixed levels that may not be compatible with the requirements of oocytes to reach optimal maturity. This is particularly related to the oocyte requirements of hormones for each stage of growth and maturity, as the collected oocytes come from follicles of different size and stages of growth. The importance of gonadotropic hormones lies in their effect on ovarian activity as a necessary factor in the production of fertile oocytes. It has been found that adding these hormones to the maturation media comes from their role in resuming the maturation process inside the body, as well they play an important role in the process of manufacturing the necessary proteins that oocytes needs during maturation, fertilization, and subsequent cell divisions of embryos (15) in addition to their effect on the expansion of cumulus cells (16). In a simple review of the vital role of these hormones:

- FSH is an essential factor for producing estradiol by playing a supporting role in the physiological events accompanying the ovulation process (17).
- LH is necessary in order to resume the meiosis before ovulation (18).
- In their study, Avery *et al.* (19) indicated the important role of FSH on the expansion of cumulus cells and follicle differentiation.
- LH contributes to controlling the manufacture of follicular steroids and the increase in the concentration of LH that appears during the final stage (20).
- In sheep, the follicular phase is accompanied by a decrease in the level of FSH in the plasma, which contributes to the final development of the oocytes (21).

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- Adding FSH to the culture media led to an increase in the fertilization capacity of *in vitro* matured oocytes, as high expansion rates of cumulus cells were observed with the presence of estradiol and LH (22).
- FSH is a key supporter of the developmental competence of oocytes obtained from immature ovaries (23).
- A close correlation ship was noticed between the resumption of meiosis and the low level of estrogen (24).
- A positive correlation was observed between rates of the blastocyst stage and estradiol concentration in the FF (25).
- The role of estradiol 17-β in cytoplasmic maturation is to activate the DNA enzymes of oocytes of the preovulatory follicle and regulate ovarian function (26).
- Several studies referred to the fixed level of 17β-Estradiol in the follicular fluid (1.5 µg/mL) (27). Accordingly, it was used in most studies with a rate not exceeding 1.5 µg/mL.
- GH has entered the world of IVEP with great power due to its important performance in reproduction and growth. Regardless of its different ovarian functions, GH improves IVF rates (28).
- GH promotes cumulus cells expansion and subsequent embryo development (29).

Recently, an important trend in IVEP technology has emerged, which is the addition of a cocktail of hormones in maturation media. Perhaps this application was of great interest due to the positive participatory effect of the hormones, for instance, the supplementation with recombinant human FSH (rFSH) and 17β-oestradiol during IVM of bovine oocytes led to an increase in embryos outcome following IVF (30). In literature, studies in cattle have postulated that the increased developmental competence of bovine oocytes in response to rFSH and estradiol occurs by the production of factors that reach the oocyte through the cell−cell coupling pathways or that the coupling per se results in physiological changes. The concentrations of hormones used in IVM varied greatly, as Table 1 shows some samples of studies that added various concentrations of hormones.

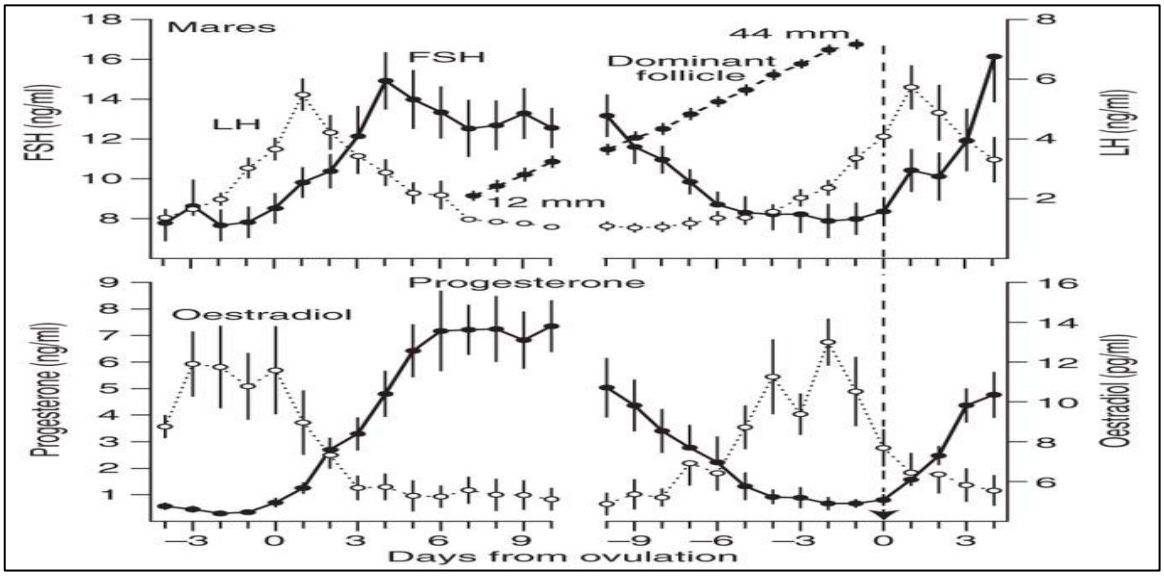

Figure 1. The temporal association of FSH, LH, Oestradiol and progesterone concentrations in the dominant follicle within the follicular wave in mares (Mean ± SE) (reproduced from [14].

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Table 1. Concentrations of some common hormones used in IVM of some studies.

Hormone	Level	Reference
GH	100 ng/ml	[31]
FSH	1 µg/ml	[32]
FSH	5 µg/ml	
LH	5 µg/ml	[8]
Estradiol	1 ng/ml	
LH	1.5 IU/mL	[33]
HCG	1.5 IU/mL	
FSH	0.075 IU/mL	[34]
FSH	0.01 IU/mL	[35]
LH	0.05 mg/ml	
FSH	15 ng/ml	[36]
LH	1 mg/ml	
Estradiol	1.0 mg/ml	
Estradiol	1 µg/mL	[37]
FSH	0.5 µg/mL	
GH	100 ng/ml	[38]

3. FCS

The serum is known as the remaining portion of blood plasma after coagulation (blood plasma without fibrinogens). It includes all the proteins that are not present in the blood clot in addition to hormones, antibodies, antigens and electrolytes. FCS is obtained exclusively from fetuses over the age of three months. In light of the ART strategies, the use of FCS as a growth medium supplement in cell culture has increased widely. In essence, the benefit of using FCS in maturation media has increased since it contains some undefined growth-promoting components such as feutin which is not available in the serum of adult animals (39). Besides, it does not contain any hormones or high levels of immunoglobulins that impede the development of oocytes in vitro (40). According to Yao & Asayama (41), FCS contains many proteins and lipids that contribute to improving cellular proliferation and survival. Here, Table 2 shows the main components of FCS according to a study conducted by Cheever et al. (42). To note, the composition of the FCS is not stable and there is wide variability in the composition which is mainly due to the species and breed as well as the geographical area. On the positive aspect, given the important role of FCS in IVM, FCS like hormones has been included as a basic additive in most studies. In literature, a wide dispersion was observed concerning the levels used. Table 3 shows specific levels of FCS (single or participant) used in some studies. Against the advantages of FCS, there are several limitations to this element. In general, some of these issues can be summarized by the following points:

FCS is highly exposed to the risk of contamination, especially viruses (41).

The occurrence of some unintended reactions while adding it to the media, would reduce the outcome (43).

From a medical point of view, FCS is thought to be part one of the carcinogenic agents (44).

The large fluctuation in FCS concentrations used in various studies eventually led to a massive dispersion in undesirable outcomes (45).

Perhaps the greatest disadvantage caused by the FCS is the relationship that arises between this element and the cryopreservation events of embryos, where a remarkable deterioration in the rates of embryo quality and survival was noticed. Obviously, this is because the FCS contains high levels of lipids, especially triglycerides (46). Through a morphological comparison between both types of embryos (frozen- thawed Vs none frozen embryos), a great difference was found in the exterior shape and structure of the embryonic cells, as the frozen- thawed embryos store a high percentage of triglycerides and a low percentage of phospholipids. Figure 2 shows the morphological differences of cells according to their lipid droplet content (47).

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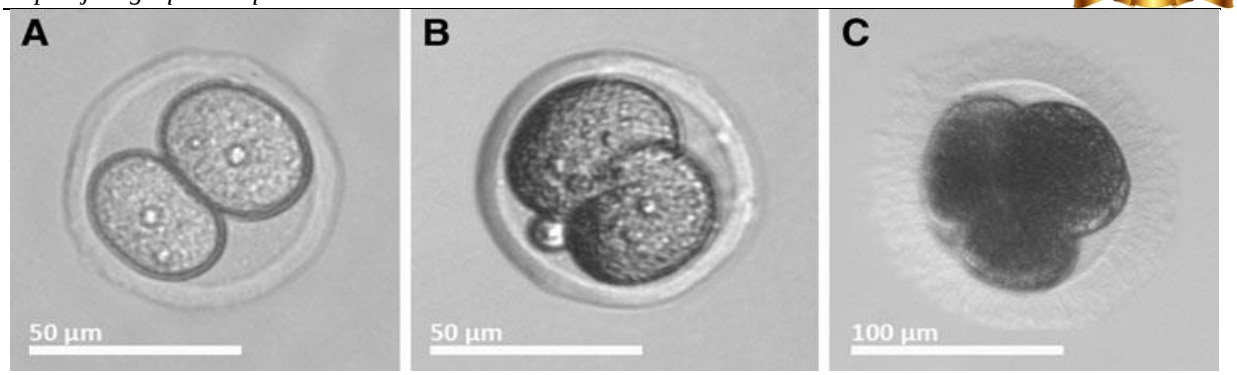

Figure 2. Light micrographs showing the contents of the blastomeres embryos of the lipid droplets, where the images show that the more opacity, the more the cell content of the lipids: (A) Wistar Albino Glaxo rat. (B) mouse. (C) cat (reproduced from [47].

Table 2. Estimates of some basic components of FCS (reproduced from [42].

Analyte	Value
Sodium mEQ/L*	132.03
Potassium mEQ/L	11.84
Chloride mEQ/L	93.37
BiCarb (HCO3) mEQ/L	16.84
Anion Gap mmol/L	33.72
Phosphorus mg/dL**	10.19
Calcium mg/dL	13.22
Magnesium mg/dL	3.09
Iron µg/dL	179.77
Creatinine mg/dL	2.49
Glucose mg/dL	102.77
Creatine Kinase IU/L	178.74
Cholesterol mg/dL	28.33
Triglyceride mg/dL	66.85
Aspartate Aminotransferase IU/L	14.21
Alkaline Phosphatase IU/L	65.17
Gamma-Glutamyl Transferase IU/L	1.14
Bilirubin, Total mg/dL	0.06
Protein, Total g/dL	0.45
Albumin g/dL	0.33
Globulin g/dL	0.16
Immunoglobulin µg/mL	135.65

*: mEQ/L: milli- equivalents per liter, **:mg/ dl: milligrams per deciliter

Table 3. Concentrations of FCS used in IVM of some studies.

Level	Reference
20%	[48]
10%	[37]
5.7%	[49]
10%	[50]
10%	[35]
10%	[36]
10%	[37]
10% and 20%	[51]
1% and 5%	[38]

4. FF

FF plays the primary regulating role in the growth and development of oocyte during the folliculogenesis stage until the oocyte acquires its developmental competence in preparation for fertilization and subsequent divisions. Nevertheless, in in vitro studies, there is widespread controversy about its usage as an in vitro additive in IVM. The biochemical constituents of FF change in a way that simulates the stages of oocytes growth. The size of FF inside the follicle is associated with an increase in the follicular size itself during the growth and differentiation as shown in the schematic representation (Figure 3) (6). According to references, the biochemical constituents of the FF show a great variety. This variation is mainly due to the animal species and the developmental stage of the follicle (follicle size). Kumar et al. (52) documented the content of the follicular fluid (hormones and growth factors) (Table 4) as well as the various biochemical constituents due to several studies (Table 5). Some major considerations deserve to be examined if this addition is included in IVM. Some studies have suggested that some biochemical constituents of the FF surrounding the oocytes in a period of growth are the factors that determine the quality and the level of subsequent developments to initiate subsequent IVF stages (53). Moreover, in the very complex follicle wave scenario, the follicles that are eligible for follow-up in development processes are determined according to a system governed by the secretion of the FSH according to specific levels of estradiol, insulin-like growth factors (IGFs), and inhibin/activin peptides (54). Based on the above considerations, the process of entering FF into IVM protocols remains a matter that depends on those constituents that inhibit the maturation. To obtain desired results, several studies recommend that the source of FF should be follicles of large size (55,56). Table 6 shows the trend of a sample of selected studies to use the FF by 10% overall.

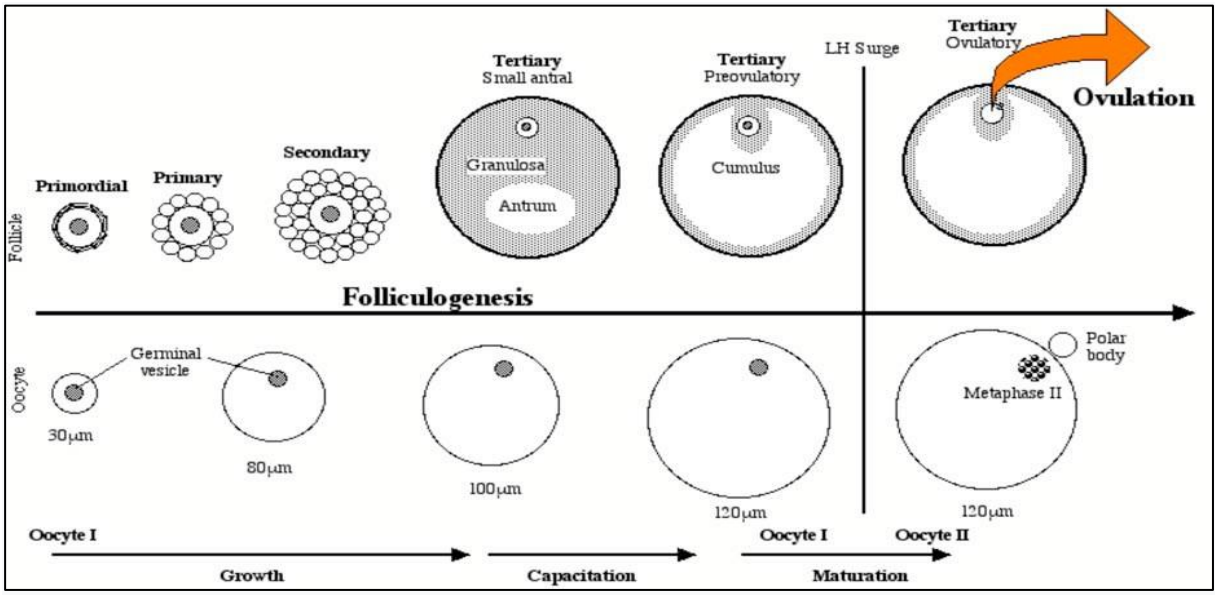

Figure 3. Schematic representation of the synchronization between development and maturation of oocytes and the expansion of the volume of FF cavity along the axis of folliculogenesis (reproduced from [6] .

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Table 4. Follicular fluid classical and non-classical hormones (reproduced from [52].

Classical hormones	Reference
Estradiol Progesterone Androgens Thyroid hormones FSH LH	[57,58]
Non-classical hormones/factors Activin Epidermal growth factor Fibroblast growth factor Follicular regulatory protein Follistatin FSH inhibitor Granulosa cell inhibitory factor Haptoglobin-like protein Hepatocyte growth factor Inhibin Insulin-like growth factor-I Insulin-like growth factor-II Insulin-like growth factor binding proteins Oocyte maturation inhibitor Oocyte maturation stimulating factor Ovine follicular fluid peptide Platelet-derived growth factor I Platelet-derived growth factor II Transforming growth factor-α Transforming growth factor-β	[58, 59]

Table 5. Metabolic and ionic concentrations of follicular fluid in cattle (Mean ± SE) (reproduced from [52].

Metabolic and ionic constituents	Follicle			Reference
	Small	Medium	Large	
Glucose (mg/dl)	40.92 ± 1.02	47.81 ± 2.14	54.44 ± 2.32	[60]
	-	-	24.9 ± 4.7	[61]
Glucose (mM)	2.01 ± 0.10	2.85 ± 0.16	3.75 ± 0.18	[53]
Total proteins mg/dl)	6.49 ± 1.34	6.78 ± 1.45	7.01 ± 1.39	[60]
	-	-	7.5 ± 0.1	[53]
	6.59 ± 0.10	6.36 ± 0.11	6.50 ± 0.10	[62]
Triglyceride (mg/dl)	33.33 ± 2.53	30.69 ± 2.23	30.24 ± 1.41	[60]
	-	-	12.7 ± 2.2	[61]
	21.8 ± 0.60	16.6 ± 0.55	12.4 ± 0.45	[53]
Cholesterol (mg/dl)	29.81 ± 2.51	25.65 ± 2.07	22.48 ± 2.23	[60]
	-	-	74.5 ± 4.5	[61]
	55.9 ± 3.39	62.7 ± 2.91	63.7 ± 3.23	[53]

Lactate (mM)	14.4 ± 0.35	9.4 ± 0.35	5.6 ± 0.37	[61]
Urea (mg/dl)	15.62 ± 1.08	16.81 ± 0.82	16.93 ± 1.25	[60]
Urea (mM)	4.65 ± 0.35	4.30 ± 0.34	4.13 ± 0.34	[53]
Iron (mg/dl)	2.16 ± 1.72	2.34 ± 1.34	2.94 ± 1.22	
Copper (mg/dl)	5.28 ± 0.49	5.32 ± 0.61	7.81 ± 1.02	[60])
Manganese mg/dl)	6.35 ± 0.74	9.71 ± 0.95	11.91 ± 0.89	
Zinc (mg/dl)	1.64 ± 0.58	2.13 ± 0.47	3.08 ± 0.72	
Magnesium(mg/dl)	-	-	5.8 ± 0.3	
Phosphate (mg/dl)	-	-	10.5 ± 0.4	
Sodium (mM)	142.5 ± 0.34	142.4 ± 0.63	141.0 ± 1.14	[61]
Potassium (mM)	10.1 ± 0.21	7.9 ± 0.28	6.0 ± 0.23	
Chloride (mM)	105.0 ± 0.50	104.0 ± 0.60	102.9 ± 0.76	
Lactate (mM)	14.4 ± 0.35	9.4 ± 0.35	5.6 ± 0.37	

Table 6. Concentrations of FF used in IVM of some studies.

Level	Reference
10%	[63]
10% and 40%	[22]
5%,10% and 15%	[64]
10%,30% and 60%	[65]
10%	[56]
10% and 20%	[66]
10%	[67]
20%	[68]
10% and 40%	[22]

5. Cysteamine

Cysteamine or b-mercaptoethanol (b-ME), is a thiolic compound with the molecular formula: C2H7NS. Cysteamine was popularly used in the 1950s as a medication that treats cystinosis. This agent is characterized by two prominent characteristics: stability and antioxidativity. Because of these two characteristics, cysteamine strongly has made its presence in the world of ART. The biochemical function of cysteamine can be summarized by contracting the harmful effects of ROS inside the cells, thus offsetting (risk neutralization) the damage caused by O2 in lipids, protein and nucleic acids during the development of early embryos (13). On the other hand, cysteamine stimulates glutathione synthesis (GSH), which in turn improves the developmental competence of oocytes (69). On the level of IVEP, two main conclusions were drawn from cysteamine usage. Firstly, cysteamine did not affect significantly the stages of nuclear and cytoplasmic maturation of oocytes (70). Secondly, cysteamine is the reason for obtaining high rates of embryos reaching the blastocyst stage (71). Meaning that cysteamine has a prolonged effect through which the oocytes gain the ability to follow up the processes of the division following fertilization. What is remarkable is that the increase in the concentrations of cysteamine above 100 µm, in fact, did not give effects worthy of consideration. Therefore, any concentration exceeding 100 µm would produce an effect almost similar to the effect resulting from adding 100 µm. Table 7 shows the concentrations of cysteamine used in some studies.

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Table 7. Concentrations of cysteamine used in IVM of some studies.

Level	Reference
25, 50 and 100 µm	[72]
10, 50 and 100 µm	[73]
50, and 100 µm	[74]
100 µm	[75]
50 µm	[76]
50,100,200, and 500 µm	[77]
100,500 µm	[78]
100 µm	[79]
100 µm	[80]

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