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Recent Advances in In Vitro Maturation (IVM): A Systematic Literature Review

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ABSTRACT

In Vitro Maturation (IVM) is one of the Assisted Reproductive Technologies (ART) that involves the retrieval of immature oocytes from antral follicles in the ovaries, either in a non-stimulated or minimally stimulated state. IVM has drawn the attention of fertility specialists due to its reliability, cost-effectiveness, low risk of Ovarian Hyperstimulation Syndrome (OHSS), and acceptable clinical pregnancy rates

Objective: Understanding the Process and Factors Influencing In Vitro Maturation of Human Oocytes (IVM)

Method: The research methodology employed in this study is the Systematic Literature Review (SLR) method. Data was collected by documenting all articles based on predetermined inclusion and exclusion criteria. A total of 10 national and international journal articles were utilized for this study, obtained from databases such as Google Scholar, PubMed, and Science Direct, using specific keywords including "In Vitro Maturation" and "human oocyte maturation". The literature search and study selection process followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Results: There were no instances of moderate-severe OHSS (ovarian hyperstimulation syndrome) in the IVM group. The fertilization rate in the group receiving growth hormone (GH) was 12.8% higher compared to the control group. Additionally, the blastocyst rate in the GH group was 9.5% higher than that of the control group. Treatment with a concentration of 50 µmol/L ALA (alpha-lipoic acid) significantly accelerated oocyte maturation. It resulted in a significantly higher mitochondrial DNA (mtDNA) copy number in mature oocytes compared to the control group (0 µmol/L ALA). The highest maturation rates were observed in human umbilical cord mesenchymal cells (hUCM) in the in vitro maturation (fIVM) of germinal vesicle (GV) oocytes, while the lowest maturation rates were observed using alpha-Minimum Essential Medium (α-MEM) in the in vitro maturation (vIVM) of GV oocytes. When AMH (anti-Müllerian hormone) was added to the IVM medium, a maturation rate of 100% was achieved in mature oocytes. The inclusion of 50 mmol/L CoQ10 in IVM media was found to reduce the level of oocyte aneuploidy by nearly 50%. The formation rate of metaphase II (MII) stage oocytes was higher in culture medium containing 1.0 mm resveratrol compared to the control group. Subsequently, a total of eight cleavage-stage embryos were frozen after intracytoplasmic sperm injection (ICSI). One year later, when the patient returned for the transfer of cryopreserved embryos, two embryos were thawed and transferred into the uterus. The patient successfully became pregnant, and the twin pregnancy progressed without complications, delivering two healthy full-term baby boys.

Conclusion: The occurrence of OHSS was not observed in any of the IVM intervention groups. Supplementation with growth hormone (GH), alpha-lipoic acid (ALA), umbilical cord-derived mesenchymal stem cells (CM-MSC), anti-Müllerian hormone (AMH), and resveratrol in the culture media each demonstrated a significant improvement in human oocyte maturation. Furthermore, resveratrol and coenzyme Q10 were effective in addressing abnormal spindle morphology, irregular chromosome arrangement, and high postmeiotic aneuploidy. It is worth noting that IVM is not exclusively limited to patients with polycystic ovary syndrome (PCOS), as it can yield satisfactory outcomes in patients with autoimmune premature ovarian insufficiency (POI).

KEYWORDS:IN Vitro Maturation(IVM), Human Oocyte Maturation, Oocyte Qiality.

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BACKGROUNDS

In Vitro Maturation (IVM) is one of the Assisted Reproductive Technologies (ART) that involves the retrieval of immature oocytes from antral follicles in the ovaries, either in a non-stimulated or minimally stimulated state. Subsequently, the oocytes are matured in vitro. The matured oocytes can then be fertilized using standard In-Vitro Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) techniques (Ho et al., 2019).

"Over the past four decades, Assisted Reproductive Technology (ART) has emerged as a vital component of treatment for many women experiencing infertility (Esteves et al., 2019). Any form of technology in which gametes are manipulated outside the body is referred to as Assisted Reproductive Technology (ART) (Begum, 1970). Ovarian hyperstimulation is required for existing Assisted Reproductive Technology (ART) techniques in order to produce a larger number of oocytes. Ovarian Hyperstimulation Syndrome (OHSS) and the cost of gonadotropins required for ovarian hyperstimulation are notable drawbacks of ART (Ho et al., 2019).

IVM has drawn the attention of fertility specialists due to its reliability, cost-effectiveness, low risk of Ovarian Hyperstimulation Syndrome (OHSS), and acceptable clinical pregnancy rates. The most suitable candidates for IVM are patients with Polycystic Ovary Syndrome (PCOS). However, IVM has indications that extend beyond just patients with Polycystic Ovaries (PCO), including poor ovarian reserve and repeated IVF failures (Hatırnaz et al., 2018).

Approximately 20-30% of oocytes obtained from stimulated cycles remain immature, and these oocytes can undergo IVM and yield good quality mature oocytes. It has been previously reported that oocytes with various patterns of cumulus cell layers are obtained during oocyte retrieval, regardless of whether it is a superovulation cycle, natural cycle, or in patients with PCO (Cha & Chian, 1998; Taylor & Pal, Lubna; Seli, 1999).

METHODS

The design of this research is a Systematic Literature Review (SLR). SLR is a term used to refer to a specific research methodology and development aimed at gathering and evaluating relevant research studies on a particular topic of focus (Triandini et al., 2019). The research methodology employed is descriptive analysis, which involves systematically analyzing collected data to provide understanding and justification for the reader's comprehensive comprehension. This method aims to review multiple journals to explore the latest research findings on in vitro maturation.

National and international journals were used as the population of researchers, selected based on inclusion and exclusion criteria. Publication article searches were conducted through Google Scholar, PubMed, and Science

Interestingly, different patterns of cumulus cell layers in IVM result in different abilities of oocyte maturation. Naturally, the ability of granulosa cells to regulate the pattern of steroid hormone secretion is largely determined by their own growth capacity (mitotic activity). During the early proliferative phase, when the growth rate of granulosa cells is high, they predominantly synthesize estrogen and produce minimal amounts of androstenedione. However, the secretion pattern changes towards and shortly after ovulation. Luteinized granulosa cells produce progesterone and estrogen. Prior to the formation of the tertiary follicle (Graafian follicle), four important changes occur as a result of the influence of Follicle Stimulating Hormone (FSH): (1) follicular fluid formation, (2) increased activity of the aromatase enzyme, (3) formation of Luteinizing Hormone (LH) receptors on granulosa cells, and (4) formation of prolactin receptors (Taylor & Pal, Lubna; Seli, 1999; Yen et al., 2019).

Along with the increasing diameter of the follicle due to the addition of follicular fluid, the process of aromatization in granulosa cells also increases, leading to the formation of LH and prolactin receptors. The influence of LH and prolactin is crucial in preparing for ovulation and progesterone production. During the preovulatory phase, follicles are more influenced by LH. Meanwhile, the activity of granulosa cells, which serve as receptors for LH, FSH, and estradiol, begins to decline. On the other hand, prolactin receptors continue to increase. The increasing activity of prolactin leads to a higher formation of LH receptors (Taylor & Pal, Lubna; Seli, 1999; Yen et al., 2019).

In several studies, the improvement of IVM protocols and modifications to IVM media have shown enhanced outcomes. However, further research is still needed to investigate all factors that influence human oocyte maturation in vitro for ART to become a standard practice. Based on the aforementioned discussion, the author is interested in conducting a focused review on human oocyte maturation through in vitro maturation (IVM).

Direct using the chosen keywords, namely "In Vitro Maturation" and "human oocyte maturation." Literature searches utilized the keywords along with the addition of the "and" notation to specify research article searches. Quotation marks (" ") were used in the database searches to ensure more specific results and were further specified by setting the publication year range.

The literature search and study selection were conducted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) strategy. After filtering based on abstract review, a total of 26 journals were identified and further filtered based on full text. From the initial total of 26 journals, during the full text review stage, 10 journals met the inclusion criteria, while the rest were excluded. The filtered journals that met the inclusion criteria were then subjected to another filtration process to assess

their quality. Journals that passed the quality assessment were subsequently analyzed.

This Systematic Literature Review utilized a narrative synthesis method, where data extracted were grouped according to similar measured outcomes to address the research objectives. Research journals that met the inclusion criteria were collected, and a summary of each journal was created, including the researchers' names, publication year, research title, methodology, and summary of findings. These journal summaries were then compiled into a table following the provided format. To ensure a thorough analysis, the abstracts and full texts of the journals were read and carefully examined. The journal summaries were then analyzed for the content related to the research objectives and the research findings. The content analysis of the journals involved coding the reviewed content based on the main points or core of each study. This was done by breaking down the content into meaningful sentences. Once the coded data were **collected, similarities and differences among the studies were identified and discussed to draw conclusions.**

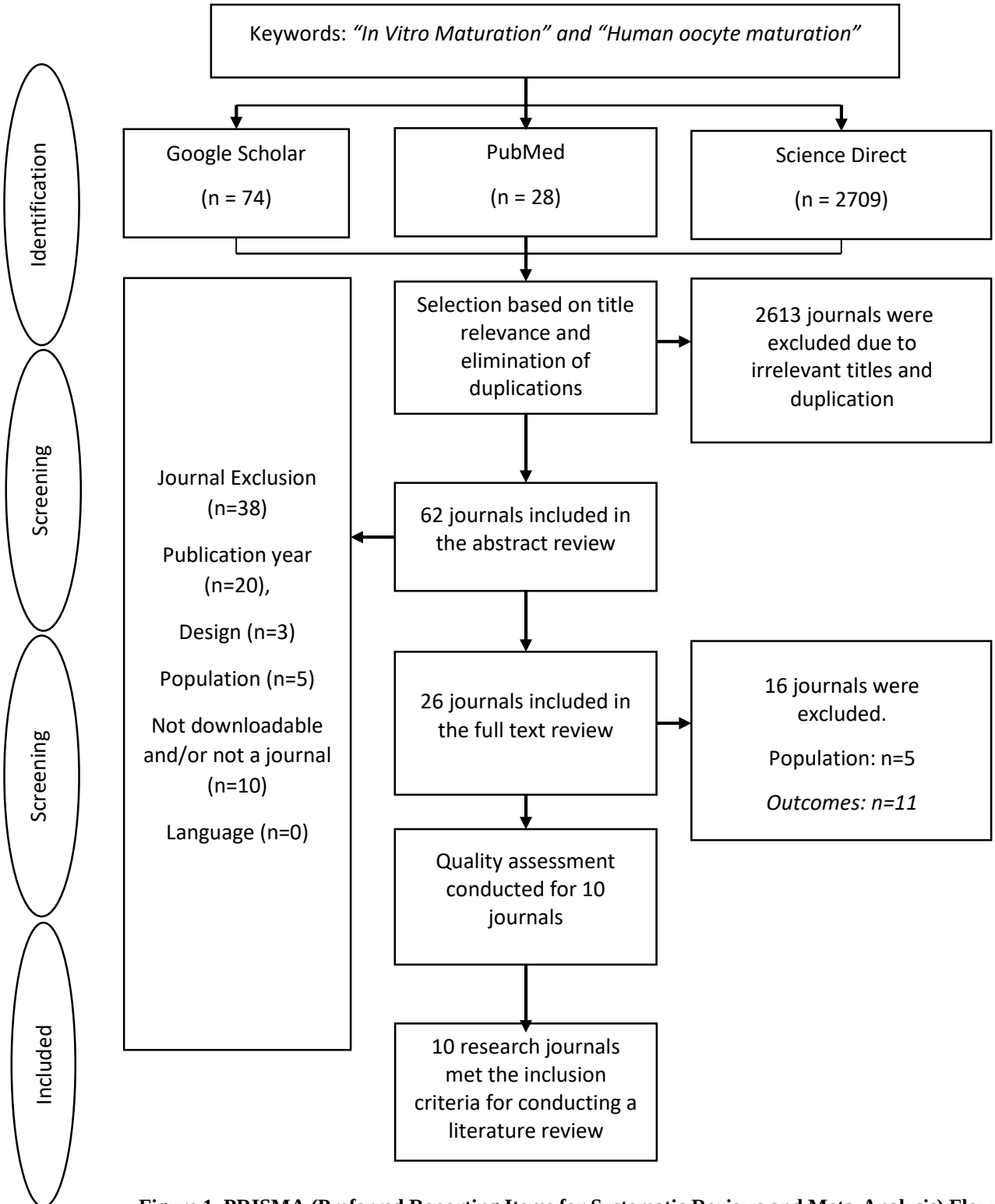

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Flowchart for Journal Selection.

RESULTS

Table 1. Summary of Data Synthesis

Author Names and Year	Title	Research Design	Subject	Results
(Zheng et al., 2022)	*In vitro maturation without gonadotropins versus in vitro fertilization with hyperstimulation in women with polycystic ovary syndrome: a non-inferiority randomized controlled trial*	*Non-Inferiority Randomized Controlled Trial*	Women with infertility between the ages of 20 and 38 years, diagnosed with PCOS using updated Rotterdam criteria and scheduled to undergo their first IVF cycle..	The research findings indicate that IVM procedure without additional gonadotropins resulted in a lower rate of ongoing pregnancies (leading to live births) within 6 months compared to standard IVF treatment. Moderate to severe OHSS did not occur in the IVM group, while in the IVF group, 10 women experienced moderate OHSS and 1 woman experienced severe OHSS. There were no statistically significant differences in the occurrence of obstetric and perinatal complications..
(Y. Li et al., 2019)	*Growth Hormon Promotes in vitro Maturation of Human Oocytes*	*Cross-Sectional Study*	The oocytes at the GV stage were subjected to ICSI (Intracytoplasmic Sperm Injection).	After obtaining the optimal concentration of GH for IVM, MII stage oocytes cultured with 200 ng/ml GH and MII stage oocytes from the control group were collected and fertilized using the ICSI method. The fertilization rate in the GH group was 12.8% higher than the control group. The blastocyst rate in the GH group was 9.5% higher than the control group.
(Hu et al., 2019)	*Preliminary Research on the Effect of Linolenic Acid on Human Oocyte Maturation*	*Experimental Study*	"Four hundred and twenty-three infertile women with husbands exhibiting male factor infertility (oligoasthenospermia, teratozoospermia, and/or azoospermia) were included in this study between October 2014 and October 2015.	Treatment with a concentration of 50 μmol/L ALA clearly accelerates oocyte maturation and results in significantly higher mtDNA copy numbers in mature oocytes compared to the control group (0 μmol/L ALA). Supplementation of 50 μmol/L ALA and FF (Group A) significantly enhances the total maturation rate compared to the FF treatment group (Group B), which exhibits a higher total maturation rate compared to Group C. However, no significant differences were observed in fertilization, embryo availability, and blastocyst production among Groups A, B, and C. ALA treatment also reduces MDA (Malondialdehyde) levels but does not affect SOD (superoxide dismutase) activity in the IVM media.
(Akbari et al., 2017)	*Mesenchymal Stem Cell-Conditioned Medium Modulates Apoptotic and Stress-Related Gene Expression, Ameliorates Maturation and Allows for the Development of Immature Human Oocytes*	*Experimental Study*	247 GV-stage oocytes were obtained from 117 patients aged 30-36 years.	The highest maturation rate was found in hUCM in fIVM (in vitro matured GV-stage oocytes), while the lowest maturation rate was observed using α-MEM in vIVM (vitrified GV-stage oocytes, then matured in vitro). The cleavage rate in fIVM was higher compared to vIVM. Additionally, the cleavage rate in α-MEM was lower than in hUCM. The developmental stage of parthenote embryos in hUCM was higher than in α-MEM. Overall, hUCM demonstrated potential efficacy in improving oocyte maturation and promoting the development and

	after Artificial Activation			expression of mRNA from BAX, BCL2, and SOD
(Bedenk et al., 2022)	*Recombinant anti-Müllerian hormon in the maturation medium improves the in vitro maturation of human immature (GV) oocytes after controlled ovarian hormonal stimulation*	*Experimental Study*	Ninety-six patients with a total of 247 oocytes, including 171 GV (germinal vesicle) stage oocytes and 76 MII (metaphase II) stage oocytes, were included in the IVF/ICSI program.	The maturation rate of oocytes reached 100% in the IVM medium supplemented with recombinant AMH alone. In comparison, a maturation rate of 68% was achieved with the use of conventional IVM medium supplemented with FSH and hCG. Furthermore, the group of oocytes matured in IVM medium supplemented with all three hormones (FSH, hCG, and AMH) resulted in an even lower maturation rate of 36%. Lastly, in the control group where oocytes were matured in IVM medium without hormone supplementation, 25% of the oocytes spontaneously matured in vitro.
(Ho et al., 2019)	*The effectiveness and safety of in vitro maturation of oocytes versus in vitro fertilization in women with a high antral follicle count*	*Retrospective Cohort Study*	Infertile women with a high antral follicle count (AFC) of at least 24 follicles in both ovaries, aged between 18 and 38 years, and who have not undergone more than one previous attempt of IVM/IVF, were included in the study. These women expressed a desire to undergo IVF/ICSI treatment.	The proportion of mature oocytes, embryos, and frozen embryos was lower in the IVM group compared to the IVF group, and the number of high-quality embryos was also lower in the IVM group. OHSS did not occur in the IVM group, while OHSS occurred in 11 women in the IVF group (moderate OHSS with a prevalence of 2.6%, and severe OHSS with a prevalence of 0.9%).
(Irez et al., 2021)	*Does the Apoptosis Value of Cumulus Cells Play a Role in Rescue Oocyte in Vitro Maturation?*	*Experimental Study*	Ninety-eight germinal vesicle (GV) oocytes with immature cumulus cells were evaluated from 30 patients (under 35 years old, excluding cases of endometriosis) after controlled ovarian hyperstimulation and oocyte retrieval.	Fifty-two percent of immature oocytes successfully reached maturation, with 56% of them being fertilized after ICSI. Among these, 39.1% reached the 3-4 cell stage on day 2, 43.4% reached the 5-8 blastomere stage on day 3, 21.7% developed into morulae, and 6.5% reached the blastocyst stage.
(Ma et al., n.d.)	*Coenzyme Q10 supplementation of human oocyte in vitro maturation reduces postmeiotic aneuploidies*	*Clinical Laboratory Observation.*	A total of 63 patients, comprising 45 patients aged 38 years and 18 patients aged 30 years, underwent the IVF program.	For women aged ≥38 years, the oocyte maturation rate in the CoQ10 50 mmol/L group was higher than in the control group. As expected, the rate of postmeiotic aneuploidy in older women (≥38 years) exceeded 50%. However, the presence of 50 mmol/L CoQ10 in the IVM media was able to decrease the aneuploidy rate of oocytes by nearly 50%. In women aged 30 years, the oocyte maturation rate and aneuploidy rate were similar, regardless of the presence of CoQ10 in the IVM media. However, the frequency of chromosomal aneuploidy was slightly lower in the CoQ10 group compared to the control,

				although the difference was not statistically significant.
(Liu et al., 2018)	*Resveratrol improves in vitro maturation of oocytes in aged mice and humans*	*Experimental Laboratory Study*	Immature oocytes from patients aged 38-45 years undergoing ICSI were included in the study.	A total of 75 GV-stage oocytes were subjected to IVM with the addition of 1.0 mm resveratrol for 24 and 36 hours. The rate of MII-stage oocyte formation in the culture media containing 1.0 mm resveratrol was higher than the control group. The percentage of spindles with abnormal morphology and chromosomes with irregular arrangement significantly decreased in the MII-stage oocytes treated with 1.0 mm resveratrol.
(Ph et al., 2020)	*In vitro maturation of oocytes for preserving fertility in autoimmune premature ovarian insufficiency*	*Case Report*	A 36-year-old amenorrheic patient diagnosed with autoimmune premature ovarian insufficiency (POI).	It was found that the size of antral follicles ranged from 2-12 mm in diameter, with a substantial level of heterogeneity. As expected, stimulation attempts using recombinant FSH (300 IU/day for 10 days) failed to induce follicle growth or increase E2 levels (serum E2 levels remained undetectable on days 6, 9, and 11 of treatment). Furthermore, serum levels of T and D4-androstenedione remained within the normal range. Two IVM cycles were performed, allowing for the retrieval of six and ten germinal vesicle (GV) stage oocytes, respectively. Within 24 hours, four and six of the GV oocytes reached the metaphase II stage. Finally, after ICSI, a total of eight embryos at the cleavage stage were cryopreserved. When the patient returned 1 year later for the utilization of the cryopreserved embryos, two embryos were thawed and subsequently transferred into the uterus. The patient became pregnant. The twin pregnancy developed without complications, and the patient successfully delivered two healthy full-term baby boys.

IVM and OHSS

The research findings indicate that the IVM procedure without adding gonadotropins resulted in a lower rate of sustained pregnancy (leading to live birth) within a 6-month, compared to standard IVF treatment (22.3% vs 50.6%). Moderate to severe OHSS did not occur in the IVM group, while in the IVF group, ten women (5.7%) experienced moderate OHSS and one woman (0.6%) experienced severe OHSS. There were no statistically significant differences in the occurrence of complications.

The proportion of mature oocytes, embryos, and frozen embryos was significantly lower in the IVM group compared to the IVF group ($P < 0.001$), and the number of high-quality embryos was lower in the IVM group. However, in the IVM group, OHSS did not occur, while moderate OHSS occurred in 8 women and severe OHSS occurred in 2 women in the IVF group (Zheng et al., 2022).

Cumulus Cell Apoptosis

There was no statistically significant difference between the levels of apoptosis in immature germinal vesicle (GV) and mature GV. Apoptosis in cumulus cells obtained from M2 oocytes was found to be lower than the apoptosis in cumulus cells from GV. The average apoptosis rate of fertilized and unfertilized GV did not show a statistically significant difference. The average apoptosis rate of fertilized GV that reached fewer than 10 blastomeres on the fifth day and GV that reached 10 or more blastomeres did not show a statistically significant difference.

The apoptosis rate did not show a significant difference between mature unfertilized germinal vesicles

(GV) and the group that was fertilized and developed into embryos. The maturation rate and formation of 2PN were 56.1% and 63.0% in all applied IVM with GV. When the fertilization rate was examined in general, it was observed to be 60% in GV oocytes and 67.2% in MI oocytes. When the apoptosis ratio of MII and immature oocytes in controlled ovarian stimulation was examined, the apoptosis rate was high in immature oocytes in the granulosa cells (Y. Li et al., 2019).

GH, ALA, CM-MSC, AMH, and Resveratrol in Oocyte Maturation

After obtaining the optimal concentration of GH for IVM, MII stage oocytes cultured with 200 ng/ml GH and MII stage oocytes from the control group were collected and fertilized using the ICSI method. The fertilization rate in the GH group was 73.1%, which was higher than the 60.3% in the control group ($P = 0.158$). The blastocyst rate in the GH group was 25.0%, which was higher than the 15.5% in the control group ($P = 0.214$) (Y. Li et al., 2019).

Therapy with a concentration of 50 µmol/L ALA clearly accelerated oocyte maturation ($P < 0.05$) and resulted in a significantly higher mtDNA copy number ($P < 0.05$) in mature oocytes compared to the control (0 µmol/L ALA). Supplementation of 50 µmol/L ALA and FF (Group A) significantly increased the total maturation rate compared to the FF treatment group (Group B), which had a higher total maturation rate ($P < 0.05$) compared to Group C. However, no significant differences were observed in fertilization, embryo availability, and blastocyst production among Groups A, B, and C. Treatment with 50 µmol/L ALA reduced MDA levels ($P < 0.05$) but did not affect SOD activity in the IVM media (Hu et al., 2019).

The increase in maturation rate was accompanied by an upregulation of GDF9 and BMP15 expression. Group C had significantly higher levels of GDF9 (Δ mean = 3.31) and BMP15 (Δ mean = 1.52) compared to Group B ($p < 0.001$; $p = 0.006$) (Haryadi et al., 2019).

After IVM was performed, the medium supplemented with recombinant AMH achieved a maturation rate of 100% (15/15). In comparison, only 68% (15/22) maturation rate was achieved using conventional IVM media supplemented with FSH and hCG. Furthermore, the group of oocytes matured in IVM media supplemented with all three hormones (FSH, hCG, and AMH) resulted in an even lower maturation rate of 36% (15/42). Lastly, in the control group, oocytes matured in IVM media without the addition of hormones, 25% (3/12) of the oocytes spontaneously matured in vitro (Bedenk et al., 2022).

The percentage of spindles with abnormal morphology and chromosomes with irregular arrangement significantly decreased in MII stage oocytes treated with 1.0 mm resveratrol ($P < 0.05$). A total of 75 GV stage oocytes from elderly patients were treated with 1.0 mm resveratrol for 24 and 36 hours. The rate of MII stage oocyte formation in the culture media containing 1.0 mm resveratrol (24 hours: 55.26%; 36 hours: 71.05%) was higher than the control group (24 hours: 37.84%; 36 hours: 51.35%).

The total number of antral follicles remained unexpectedly normal (24 and 22 follicles). It was found that the size of antral follicles ranged from 2 to 12 mm in diameter, with substantial heterogeneity. Additionally, as expected, the stimulation trial using recombinant FSH (300 IU/day for 10 days) failed to induce follicle growth or increase in E2 levels (serum E2 levels on days 6, 9, and 11 of treatment remained undetectable). Furthermore, serum levels of T and D4-androstenedione remained within the normal range. Two IVM cycles were performed, allowing the aspiration of six and ten germinal-vesicle stage oocytes, respectively. Within 24 hours, four and six of them reached the metaphase II stage. Finally, after ICSI, a total of eight cleavage-stage embryos were cryopreserved. When the patient returned 1 year later for the utilization of the cryopreserved embryos, two embryos were thawed and subsequently transferred to the uterus. The patient became pregnant, and the twin pregnancy developed without complications. The patient successfully delivered two healthy full-term baby boys (Liu et al., 2018).

Coenzyme Q10 in its role in reducing postmeiotic aneuploidy

The study on women aged ≥38 showed that the oocyte maturation rate in the CoQ10 50 mmol/L group (82.6%) was significantly higher than in the control group. As expected, the postmeiotic aneuploidy rate in older women (≥38 years) was very high (65.5%). However, the presence of 50 mmol/L CoQ10 in the IVM media resulted in an oocyte aneuploidy rate of 36.8%. Similarly, the frequency of chromosome aneuploidy (number of aneuploid chromosomes/total number of chromosomes analyzed) in the CoQ10 group was significantly lower than the control group in older women (4.1% vs 7.0%).

In women aged 30 years, the oocyte maturation rates were similar with or without CoQ10 in the IVM media (80.0% vs 76.9%). The oocyte aneuploidy rates in this group were also similar with or without CoQ10 (28.6% vs 30.0%). However, the frequency of chromosome aneuploidy was slightly lower in the CoQ10 group compared to the control (2.3% vs 3.5%), although the difference was not significant.

DISCUSSION

Oocyte maturation in IVM is lower compared to standard IVF, but the side effect of moderate to severe OHSS (Ovarian Hyperstimulation Syndrome) is found in the IVF group. OHSS is one of the complications that can occur in women undergoing fertility treatment. This condition is characterized by an abnormal and excessive ovarian response to medications during stimulation.

A study conducted by Yue et al. (2019) on infertile women aged 20 to 38 years who were diagnosed with PCOS using updated Rotterdam criteria and scheduled to undergo IVF cycles, showed that IVM procedure without additional gonadotropins resulted in lower ongoing pregnancy rates

(leading to live birth) within 6 months compared to standard IVF treatment (22.3% vs 50.6%). Moderate to severe OHSS did not occur in the IVM group, while in the IVF group, ten women (5.7%) experienced moderate OHSS and one woman (0.6%) experienced severe OHSS. There was no statistically significant difference in the occurrence of complications.

This is consistent with a prospective multicenter cohort study conducted in three non-academic hospitals in the Netherlands. The study subjects included 45 women who had undergone at least one IVF or ICSI cycle, while 18 women had undergone ovarian induction (OI) with or without intrauterine insemination (IUI). A total of 81 IVF cycles were initiated by them, of which 41 were canceled. Out of these 41 cycles, 32 were discontinued due to threatening OHSS, and 9 were discontinued due to insufficient follicle growth. Most of the cycles were terminated due to anticipated OHSS (Ho et al., 2019).

This supports the notion that IVM can reduce the incidence of Ovarian Hyperstimulation Syndrome (OHSS) in women undergoing fertility programs, as the ovarian stimulation required in conventional IVF is minimized or even unnecessary in IVM. However, the oocyte maturation rate in IVM is lower compared to conventional IVF.

Apoptosis rates did not show significant differences between unfertilized mature germinal vesicles (GVs) and those that developed into embryos. Apoptosis is regulated by the activation of several genes encoding caspase proteins, which are cysteine proteases that become active during cell development and signal cell destruction. It is hypothesized that the addition of FRBI can inhibit the regulation and activation of apoptosis-inducing factors. GV breakdown (GVBD) likely occurs through an indirect action mediated by cumulus cells. This mechanism involves luteinizing hormone (LH) inducing the disruption of communication between the oocyte and cumulus cells, thereby halting the flow of regulatory molecules into the oocyte. This induction is also likely mediated by the IP3/Ca2+ pathway.

This study found that supplementation or additions to the culture media can influence oocyte maturation in humans. Growth hormone (GH) significantly influences ovulation regulation and fertility, although the exact mechanisms are still not fully understood. Deficiency in GH (GHD) is associated with lower fertility, and GH receptor (GHR) and GH mRNA have been found in human follicle development. (Devesa & Caicedo, 2019). The addition of GH to the media increased fertilization rates, with a fertilization rate of 73.1% in the GH group, higher than the 60.3% in the control group. These findings are consistent with a study by J. Li et al. (2020), where patients in the GH group received 3 IU of recombinant GH per day, starting from the early decline in receptor numbers for long protocol or stimulation for antagonist protocol until the day of hCG trigger. It was found that compared to the control group, the GH group showed significantly better clinical outcomes in terms of implantation rate, clinical pregnancy rate, ongoing pregnancy rate, and live birth rate per cycle initiation or per embryo transfer. Additionally, it was found that the GH group had significantly higher rates of ongoing pregnancy and live birth in fresh and frozen cycles. In this study, no negative effects associated with the use of GH were observed (J. Li et al., 2020).

Therapy with 50 mmol/L ALA accelerates oocyte maturation, but this effect is limited to fertilization, embryo availability, and blastocyst production. This has been demonstrated through research conducted on female mice in vitro with various interventions in their culture media. Exposure of oocytes to omega-3 up to 10 μg/ml resulted in lower rates of oocyte degeneration, while exposure to omega-3 up to 100 μg/ml caused higher rates of oocyte degeneration compared to the control group. The proportion of oocytes in the GV stage was significantly lower in the groups exposed to 10 and 100 μg/ml omega-3 compared to the control group. Adding omega-3 (10 and 100 μg/ml) to the oocyte culture environment resulted in a significant decrease in the proportion of oocytes arrested at the MI stage and a significant increase in the proportion of oocytes arrested at the MII stage compared to the control group (M et al., 2020).

This effect is closely related to changes in FA metabolism. In oocytes, fatty acid β-oxidation (FAO) is the main source of energy for oocyte maturation and early embryo development. Additionally, FAO in cumulus cells provides crucial support during oocyte maturation. (Marei et al., 2017)

The highest maturation rate was found in hUCM in fIVM (in vitro matured GV oocytes), and the lowest maturation rate was observed using α-MEM in vIVM (GV oocytes vitrified and then matured in vitro). The cleavage rate in fIVM was higher than in vIVM. Additionally, the cleavage rate in α-MEM was lower compared to hUCM. The parthenote embryo development stage in hUCM was higher than in α-MEM. Overall, hUCM demonstrated potential efficacy in improving oocyte maturation and promoting the development and mRNA expression of BAX, BCL2, and SOD. (Akbari et al., 2017)

The paracrine effects of stem cells on folliculogenesis, which include trophic effects (anti-apoptosis, mitotic stimulation, and proliferation), immunomodulation, angiogenesis, anti-scarring effects, chemotaxis, induction of differentiation, and sometimes fusion with target cells, provide the basis for the development of this technique. All of these effects have the potential to accelerate oocyte maturation. Incubation for 24 hours with the addition of 50% CM-MSC (conditioned medium from mesenchymal stem cells) was able to increase the rate of oocyte maturation, as evidenced by increased levels of GDF9 and BNP15 (Haryadi et al., 2019). High levels of oocyte maturation were achieved when conditioned medium (CM) was used as the culture media, as demonstrated in previous studies by Ling et al. (2008). However, these studies were limited to oocyte maturation alone, indicating the need for

further research to demonstrate the positive effects of adding CM-MSC to the culture media on fertilization.

The addition of recombinant anti-Müllerian hormone (AMH) to the culture media has significantly improved oocyte maturation by 100% compared to conventional IVM (with the addition of FSH and hCG) or the combination of these three hormones. These results were obtained in human oocytes. In this study, in vitro matured oocytes were denuded using hyaluronidase to remove the granulosa cells. It was confirmed that the AMHR2 protein and mRNA encoding were expressed in human oocytes. The co-expression of mRNA and protein allows us to conclude that oocytes may synthesize their own AMHR2, which is a completely novel finding.

Consistent with the study by Yang et al. (2017), it was found that AMH does not prevent follicle formation when added to cortical pieces taken from mid-pregnancy ovaries before the initiation of in vivo activation. AMH was also present in this experiment at low concentrations (0.7-7.1 nM), which aligns with the levels found in the follicular fluid of small antral follicles in cows, sheep, and goats. (Yang et al., 2017)

The percentage of spindles with abnormal morphology and chromosomes with irregular arrangement significantly decreased in MII stage oocytes treated with 1.0 mm resveratrol. Additionally, 50 mmol/L Coenzyme Q10 in IVM media increased oocyte maturation in women aged ≥ 38 years, where the rate of postmeiotic aneuploidy is particularly high. CoQ10 can improve structural defects in spindles and chromosomes that develop with advancing age. To protect the maternal chromosomes from disturbances caused by sperm entry, a thick layer of actin filaments accumulates beneath the oocyte cortex in newly ovulated oocytes. Aging oocytes are found to have lost their actin cap, but supplementation with CoQ10 can partially prevent these abnormal disruptions (Zhang et al., 2019)

CONCLUSION

The majority of the articles in this systematic literature review use experimental design as their primary research method, where the subject has minimal impact on the method's efficacy and the researcher has strong control over the variables to obtain desired results. Two of the ten articles confirmed that IVM (In Vitro Maturation) as an alternative to Assisted Reproductive Technology (ART) has shown its role primarily in addressing side effects, such as the occurrence of OHSS, which is not observed in any of the intervention groups using IVM. In IVM, supplementation or addition of products to the culture media can be performed, which, based on research results, have provided satisfactory effects on oocyte maturation rates. The results have been validated by six out of ten articles that investigated the issue. Supplementation with GH, ALA, CM-MSC, and AMH, respectively, has shown significant improvements in human oocyte maturation. Furthermore, abnormal spindle morphology, irregular chromosome arrangement, and high postmeiotic aneuploidy can be treated using resveratrol and coenzyme Q10.

However, this research has certain limitations that can serve as ideas for future studies. Based on the research findings, the researchers propose suggestions regarding the generated analysis. It is recommended for future research to explore how to enhance human oocyte maturation using in vitro maturation (IVM). This is done to further support IVM in terms of oocyte maturation, as the maturity ratio is still lower than that of IVF. Additionally, it can reinforce IVM as an alternative to ART that yields satisfactory results.

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