



The Major Factors Affecting Oocyte Quality in IVF Cycles: A Narrative Review

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Abstract

Background: The role of assisted reproductive technologies, including in-vitro fertilization [IVF], is increasing daily because of the significant rise in subfertility cases. Among women, the most observed causes of infertility are primary ovarian insufficiency and premature ovarian failure, accounting for 25% of cases, followed by tubal damage (20%) and uterine abnormalities (10%), all contributing to the increase in IVF cases among couples. The success of IVF depends on various factors; however, the role of oocyte quality and maturation level is considered a pivotal cardinal factor for the success rates of IVF.

Methods: A thorough literature analysis was performed using the following search terms: "Oocyte Quality" and "IVF cycle." The databases searched included PubMed, Google Scholar, MEDLINE, Cochrane Library, and ResearchGate.

Discussion: IVF success rates especially depend on oocyte quality and level of maturation. Several factors affecting these two factors include obesity, which increases O₂ and H₂O₂ levels resulting in elevated endoplasmic reticulum [ER] stress; Polycystic Ovary Syndrome [PCOS]; age; endometriosis; cyclic nucleotides used in IVF; thalassemia major which is associated with lower ovarian reserve and increased redox activity malignancies, and anti-neoplastic drugs, which may contribute to premature ovarian insufficiency. Various treatment options were proposed to improve oocyte quality and maturation level, including growth hormone [GH] supplementation alongside ovarian supplementation, autologous mitochondrial transfer, luteal phase ovarian stimulation, administration of MI-Melatonin-Vitamin D₃, Duphaston, and putrescine supplementation.

Conclusion: With the rising number of subfertility cases, the importance of Assisted Reproductive Technologies [ART] is growing. The success rate of IVF on oocyte quality and level of maturation level, and few with several factors affecting these. Though numerous treatment options have been proposed to enhance oocyte quality and maturation, not all have been deemed beneficial.

Keywords: Oocyte Quality, IVF cycle, Obesity, Age, Endometriosis, PCOS, cAMP analogs, Thalassemia, Markers, Malignancies

Introduction

The role of assisted reproductive technologies [ART], specifically in-vitro fertilization [IVF], is on the rise due to a substantial increase in subfertility cases [1]. Subfertility is a delay in unwanted conception [2]. The World Health Organization reports that one out of six individuals have infertility [3]. In women, primary ovarian insufficiency and premature ovarian failure are the most observed causes of infertility, accounting for a quarter of the cases. This is followed by tubal damage (20%) and uterine abnormalities (10%), which contribute to the rise in IVF cases among couples [5]. IVF's success depends on various factors; however, oocyte quality and maturation level are fundamental for enhancing IVF success rates.

A critical factor of IVF is triggering oocyte maturation before retrieval and fertilization [6]. In the process of ovarian stimulation, not all eggs produced are at the same stage of development, leading to variations in maturation and retrieval time [7]. During an IVF cycle, as many as 30% of the collected eggs may not be fully matured. Therefore, reducing the number of immature eggs is important to increase the success rate of the IVF procedure [8]. In standard IVF cycles, a single injection of human chorionic gonadotrophic hormone (hCG) is typically used to trigger the release of mature eggs. However, it's not well understood why some eggs remain immature during this process. These immature eggs may come from small follicles collected during the egg retrieval process or larger follicles that don't respond appropriately to the hCG injection [8].

Some oocytes might resist stimulating hormones, while prolonged exposure of sensitive oo-cytes to hCG can lead to ovarian hyper-stimulation syndrome [OHSS] and a potential risk of IVF cancellation [9]. To prevent the occurrence of OHSS, the combination of Gonadotropin-releasing hormone (GnRH) agonist and hCG is effective in promoting egg maturation. Starting the stimulation process with GnRH agonists reduces the risk of OHSS, and

adding hCG helps to support luteal function [6].

Another important factor in IVF success is oocyte quality. Ovarian aging is due to the progressive reduction of the amount and quality of ovarian reserve, which may predict the duration of a woman's reproductive lifespan. Diminished ovarian reserve (DOR) is associated with reduced fertility rates and a weaker response to ovarian stimulation in the context of IVF treatment [10].

Age is a crucial factor affecting both the quality of eggs and the ovarian reserve. However, there is limited knowledge regarding the differences in egg quality, pregnancy, and clinical outcomes between young and older women with DOR, complicating common assumptions. Ovarian reserve is typically evaluated based on age, baseline follicle-stimulating hormone (FSH), baseline antral follicle count (AFC), and baseline anti-Mullerian hormone (AMH) levels [6]. AMH, a glycoprotein belonging to the transforming growth factor-b (TGF-b) super-family, is primarily produced by granulosa cells surrounding pre-antral and small antral follicles in women [11]. It plays a role in regulating folliculogenesis activation [12]. Similarly, some studies have also negated the positive impact of AMH in providing good-quality oocytes during the IVF cycle [13]. In this narrative review, we aim to explain the different factors that influence the quality of oocytes based on existing literature.

Methods

Study Duration

From September 2021 until December 2022.

Study Design

A critical analysis of the literature regarding "Oocyte Quality in IVF Cycles" was done through the identification of published research works on this specific topic.

Data collection technique

A thorough literature review was done to identify studies that describe our topic of

interest using the following search terms: “Oocyte Quality” and “IVF cycle.” Databases searched included PubMed, Google Scholar, MEDLINE, Cochrane Library, and ResearchGate. Articles were excluded if they were case reports and letters to the editor. Then, an objective analysis of the published works was conducted to describe and synthesize the available literature, providing a conclusion from this evidence.

Discussion

1. Age Affecting Oocyte Quality

Oocytes within the ovaries undergo development in utero; from that point onward, their quantity continuously declines. In addition, with age, the quality of oocytes decreases, ultimately diminishing natural fertility in older females, starting in the mid-thirties [14]. Cellular changes occurring in aging oocytes, including a less qualified cytoplasm and a high rate of genomic abnormalities, are among many other factors that affect oocyte quality [15]. Chromosomal and mitochondrial abnormalities in newborns can be the result of these changes that take place in older women [16].

The process of aging disrupts meiotic spindle formation and chromosome alignment. For instance, cohesin, a protein that binds sister chromatids, is supposed to cleave during separation. However, aging increases the frequency of separation errors, leading to chromosomal abnormalities [17].

Moreover, with age, telomeres that protect the DNA as cap-like sequences become shorter, causing a decrease in telomerase activity [18]. This exposes the DNA and increases the risk of damage that can affect the normal process of meiosis.

Additionally, it was found that DNA repair decreases with age, given the downregulation of RAD-50 and RAD-17 genes in older oocytes and a decrease in antioxidative enzyme levels [19].

Age related changes extending to mitochondrial DNA, mitochondrial gene expression, and mitochondrial membrane potential. These alterations collectively

affect mitochondrial functioning, accumulating mutational loads in mitochondrial DNA, reduced ATP production, and subsequent aneuploidy, contributing to compromised oocyte quality [20].

2. Obesity Affecting Oocyte Quality

Besides affecting the body's metabolic processes, obesity negatively affects female fertility. Chronic inflammation influences the entire body and specific tissues and oxidative stress [OS] contributes to adverse effects on the ovaries [21].

Several studies have shown that compared to women with average weight, women with a high BMI tend to develop low-quality oocytes, reduced pre-implantation rates, increased risk of miscarriage, and reduced responsiveness to gonadotropins [21]. This reduced responsiveness can be solved by stimulating the ovaries with exogenous gonadotropins [22, 23]. This technique, although exogenous gonadotropin stimulation would not resolve low-quality oocytes, pre-implantation rates, and miscarriages, can enhance ovarian responsiveness among obese individuals, it does not fully counteract the miscarriage risk, pre-implantation rates, and low-quality oocyte [24]. The poor oocytes can negatively affect fetal development [25].

This phenomenon is based on increased O₂ and H₂O₂, which results in a higher OS state. The endoplasmic reticulum [ER] will consequently activate unfolding protein responses [26]. The rise in ER stress markers would critically reduce ovulation, fertilization, and pre-implantation. Hence, manifests as a decline in oocyte quality [27, 28].

To demonstrate the effect of ER stress on oocytes, Wu et al. (2012) administered thapsigargin, an ER stressor on cumulus-oocyte complexes [COC]. This treatment led to a decrease in cell expansion, proving a sign of lower-quality oocytes and a slower rate of development. Besides inducing ER stress, thapsigargin causes a decline in the mitochondrial membrane potential.

Following the application of this treatment, the COCs were cultured while salubrinal was present, which counteracted the impact of thapsigargin. Salubrinal was utilized as an inhibitor of endoplasmic reticulum (ER) stress to illustrate that ER stress adversely affects the quality of oocytes [29]. Likewise, Sutton-McDowall et al. (2015) treated the COCs with palmitic acid, which has similar effects as thapsigargin, decreasing the cumulus expansion and reducing the oocyte quality [27].

3. Endometriosis Affecting Oocyte Quality

The mechanism behind endometriosis-related infertility remains largely unknown [30]. Various causes have previously been involved: anatomical abnormalities, tubal occlusions, endometrial receptivity, and oocyte maturation have been involved. Nevertheless, unexpectedly, no comprehensive review of the available literature has been made to demonstrate or deny how endometriosis might affect the quality of an oocyte, whether clinically or biologically [31].

General morphological changes, such as cytoplasmic granularity, the presence/absence of vacuoles, assessment of the surrounding oocytes by the cumulus cells, and the constitution of follicular fluid (FF) are the first parameters in determining oocyte quality. When oocytes are obtained from females known to have endometriosis and investigated, it has been shown that they possess an increase in cortical granule loss, as well as a zona pellucida (ZP) thickening, which might affect the process of fertilization, with the disbanding of ZP and the following hatching and implantation done by the embryo. Moreover, when it comes to studies on In Vitro Maturation [IVM], there are fewer germinal vesicles (GV) and oocytes that can reach meiosis II in patients known to be affected by endometriosis compared to equivalent controls [32]. It was also shown that the dysmorphism characterizing oocytes, or the possession of a dark central granule within the cytoplasm, was more frequent when comparing females with endometriosis to the control group [33]. In

addition, oocyte spindle morphology and the quantity of mature oocytes were not significantly different between the controls and females with endometriosis [34, 35].

The cytoplasmic contents include the follicular fluid, the oocyte cytoplasm, vacuoles, and Smooth ER. These are important in oocyte competence and embryo development [36]. It was shown that oocytes from females with endometriosis had an increased quantity of oocytes with more dispersed chromatin and bulky nucleoli than controls. In addition, a lower number of mitochondria and a higher proportion of mitochondrial abnormalities, described as having small, swollen, or blurred vacuoles, were seen in oocytes from female patients known to have endometriosis versus their controls, which in turn led to a lower number of mitochondrial DNA (mtDNA) [15]. These observations further proved that low mtDNA content could predict decreased oocyte quantity in women [37].

A meta-analysis of IVF success rates showed a decreased rate of fertilization in females with endometriosis (odds ratio (OR) of 0.81 with a 95% confidence interval (CI)) compared to numerous other reasons for infertility, such as male and tubal factors or ovulatory dysfunction, supporting that endometriosis is the most critical factor in decreasing the number of oocytes and thus leading to a decrease in the success of fertilization [38]. Another review showed that women with endometrioma had 150% less quantity of retrieved total oocytes and 361% less quantity of MII oocytes compared to wild type. However, no difference in fertilization rates was noted between endometrioma-containing ovaries and their contralateral healthy ones [39]. Finally, Harada et al. compared IVF results in the ovary after endometriosis resection with the contralateral ovary and found that the number of retrieved oocytes decreased after excision of an endometrioma ($p=0.009$) but with a similar fertilization rate [40].

Besides, endometriosis is correlated with a decreased mature oocyte quantity that

could be retrieved relative to other infertility reasons [20]. In addition, oocytes retrieved from women with endometriosis have more chance of a changed morphology and a reduced number of mitochondria within the cytoplasm relative to infertile women for other reasons [20].

4. Endometriosis Markers

Despite being a prevalent cause of infertility in females, the development of endometriosis is not yet comprehensively understood. Endometriosis causes interference with the microenvironment surrounding follicles. Hence, a lower oocyte quality, along with disruptions in ovulation and lower fertilization and implantation rates, will be observed [41]. The research by Kumar et al. revealed that the number of oocytes in endometriosis patients was lower than in the control group. Their quality was also significantly decreased. Additionally, based on Wu et al.'s study, the quantity and quality of oocytes of patients undergoing IVF and having endometriosis were negatively affected [42].

There is a suggestion that OS may be linked to endometriosis [43–47] by an increase in reactive oxygen species [ROS] production or altering detoxification routes inside the peritoneal cavity [48]. Studies suggest that high levels of ROS can cause chromosomal instability and meiotic abnormalities, leading to a decrease in oocyte quality [49]. Patients with moderate to severe endometriosis undergoing IVF have been found to have higher levels of pro-inflammatory cytokines, such as IL-8 and IL-12, within the follicles, which is also associated with lower oocyte quality [50]. Furthermore, local inflammation and toxic substances like free iron from endometrioma cysts can decrease embryo quality [13].

Therefore, identifying inflammatory biomarkers such as ROS and pro-inflammatory cytokines is essential in assessing and treating women with endometriosis, particularly those undergoing IVF.

5. AMH Marker

Anti-mullerian hormone [AMH], secreted by granulosa cells in preantral and antral follicles, is a widely used marker for assessing ovarian reserve in assisted reproduction. Reduced numbers of growing follicles are often followed by decreased circulating AMH levels, which reflect the ovarian follicular pool [51]. Although one study suggested a potential relationship between AMH concentrations and oocyte quality in IVF-ICSI based on successful embryos available for transfer, [52] more recent studies with larger sample sizes and controlled factors have shown that AMH concentration is not related to oocyte quality at any age [13, 51, 53].

6. Cyclic Nucleotides Affecting Oocyte Quality

Using cyclic nucleotides in IVM has a practical application in ART [54]. IVF protocols that cAMP mediates have resulted in better quality oocytes compared to standard IVM methods. This improvement in oocyte quality has been measured by an increase in subsequent pre-implantation embryo development and overall quality [34].

7. Thalassemia Affecting Oocyte Quality

Recent studies revealed that thalassemia major decreases ovarian reserve. Patients with this disease have lower levels of AMH and Antral Follicular Count [AFC] [55, 56].

In addition, evidence showed an increased level of redox activity in the follicular fluid of the beta-thalassemia major patient, which suggested that iron overload due to repeated blood transfusion affects ovarian reserve directly by its redox activity in oocyte follicular fluid [57]. To elaborate further, iron causes an increase in the Reactive Oxygen Species [ROS], a significant regulator of the OS. Hence, frequent transfusions will negatively impact the competence of a woman's oocytes [58]. Despite what has been said, another retrospective study proved the opposite, where no impact was seen on the oocyte quality. However, iron had no association with the quality of a woman's oocytes. One limitation to

consider, however, is that this specific study targeted a small population without measuring the pregnancy rate [59].

It is important to note that even in non-transfusion-dependent thalassemia [NTDT], two central mechanisms trigger the production of ROS. To begin with, a shortage of oxygen due to anemia or ineffective erythropoiesis destroys the mitochondria, triggering ROS release. In addition to that, thalassemia patients suffering from hemochromatosis cause an increase in iron absorption, which also triggers the production of ROS [60].

8. Malignancies Affecting Oocyte Quality

Cancer's impact on the quality of oocytes is still a matter of debate. Some studies have shown that cancer negatively affects the quantity of oocytes, especially in patients undergoing controlled ovarian hyperstimulation [COH] [61, 62]. On the contrary, other studies have proven no correlation between cancer and oocyte quantity or morphology [63]. A prospective study that included 82 cancer patients and 180 controls reported that cancer does influence the ovarian response, particularly the quality of oocytes, during COH performed for fertility preservation. Nonetheless, cancer patients and the control group with similar quantities of oocytes retrieved were also matched by age. It should be noted that the study's results were limited by different triggering drugs being used, the inability to report pregnancy outcomes due to the storage of those oocytes, and the small number of patients recruited for the study. All these factors were essential in avoiding the ovarian response for different cancers [64, 65].

Premature ovarian insufficiency (POI) and infertility are potential consequences of anti-neoplastic drugs because chemotherapeutic and radiotherapeutic agents can significantly reduce ovarian reserve. Activating primordial follicles and the apoptosis process causes an increase in inflammation, which indirectly degenerates growing follicles and destroys blood vessels, which can negatively affect the quality of

oocytes [66, 67]. The risk of oocyte injury depends on various factors, including the type and cumulative dose of chemotherapeutic agents and whether or not radiotherapy is administered [68]. Scientists have been researching many compounds as potential protective agents against these adverse effects over the past two decades, with current debates surrounding using GnRH analogs as a protective agent. Two meta-analyses and systematic reviews, one of which included 11 randomized controlled trials (RCTs) and 7 cohort studies and the other of which 10 RCTs, concluded that developing POI after gonadotoxic chemotherapy can be avoided by providing GnRH synchronically. However, several limitations were found in those studies, including differences in the methodology section, small sample size, different diagnoses, treatment regimens, and no follow-up. As a result, it isn't easy to draw definitive conclusions about the magnitude and duration of GnRH analogs' efficacy [9, 65, 69]. A meta-analysis of five RCTs and 873 patients focused on premenopausal patients with early breast cancer undergoing chemotherapy provided evidence for the safety and efficacy of short-term inhibition of ovaries with GnRH analogs. This intervention is considered an option to reduce the likelihood of chemotherapy-induced POI and potentially improve future fertility [9]. Despite that, two meta-analyses [69] and systematic reviews [9] concluded that GnRH analogs do not appear to protect the ovaries from gonadal toxicity [70, 71, 72]. The systemic review's results were limited as it only included RCTs in the English language, a small sample size, and random models, lowering the statistical power [9]. Similarly, the meta-analysis's results were limited as one of the most prominent included studies had significant methodological flaws [69].

AMH, Granulocyte-colony stimulating factor (G-CSF), and Multi-drug resistance gene 1 (MDR1) are the protective agents investigated in rodent models, particularly in mice. Studies have highlighted their potential as a protective agent against

chemotherapy-induced follicular loss in rodents, but there is a lack of research on their effects on humans [67, 73]. Surgical procedures are also employed to maintain fertility and preserve oocyte quality. In 2013, the American Society for Reproductive Medicine (ASRM) approved mature oocyte cryopreservation as a fertility preservation method and no longer deemed it experimental [74]. Further studies have supported oocyte cryopreservation as the first line and most reputable fertility preservation option for cancer patients undergoing treatment [75, 76].

Ovarian transposition (oophoropexy) is another protective surgical procedure that involves gonadal mobilization from a radiation spotlight to a safer radiation therapy-free zone in patients receiving abdominal or pelvic radiation therapy [77, 78]. There was a wide variation in the reported success rates of ovarian transposition in preventing ovarian failure, ranging between 16% and 90%. This variation was suggested to be mainly due to scattering radiation and ovarian vascular change caused by surgical procedures in the separation of mesovarium and utero-ovarian ligament [8, 76]. If radiotherapy involves whole-body radiation or is combined with chemotherapy, oophoropexy would not be a helpful approach [9, 69]. While many studies have described oophoropexy as a safe and effective method for preventing premature ovarian failure and enhancing fertility in cancer patients, longer follow-up is necessary to evaluate ovarian function after cancer treatment [79, 80]. Overall, there is consensus in the literature that the effect of malignancies and their therapeutic agents on oocyte quality needs further investigation.

9. PCOS Affecting Oocyte Quality

The exact explanation of the effects of polycystic ovary syndrome (PCOS) on oocyte quality is still challenging and dependent on the disease's phenotypic presentation [81]. Principally, PCOS, with or without metabolic comorbidity, is associated with a chronic inflammatory state unfavorable for folliculogenesis.

Furthermore, PCOS oocytes express some intrinsic intrafollicular abnormalities that might render the oocyte lower quality [71].

The more complex issue is the association of other comorbidities with PCOS, such as Hyperandrogenism (HA), insulin resistance (IR), and obesity. Solely, each one of these has its effect on oocyte quality. For example, a review differentiating between PCOS patients with and without obesity demonstrated that patients with higher BMI had increased levels of palmitoleic acid and oleic acid compared to those without obesity. These acid levels are correlated with the oocyte developmental competencies. Thus, it might explain the poorer oocyte quality and inferior pregnancy outcomes in PCOS patients. Moreover, IR may cause a decrease in the oocyte's glucose uptake, thus decreasing its energy resource, indirectly affecting the oocyte quality [82].

On the molecular level, Nikbakht et al. (2021) stated that genes and molecules correlated with an increase in OS are more expressed in the oocytes of PCOS patients than those without PCOS [83]. This OS led to poor oocyte quality. Furthermore, Gohari Taban S. Et al. (2021) stated that ADAMTS-4 and ADAMTS-5 in the human cumulus cells (CCs) of PCOS patients are downregulated. These proteoglycanases are responsible for progesterone receptor (PR) expression. Therefore, PR expression on oocytes is decreased in PCOS patients leading to lower oocyte quality. The latter might affect these patients' fertilization rate in ART cycles [84].

A study conducted by Nikbakht R. et al. in 2021 revealed that although the number of oocytes retrieved in ART cycles of patients with PCOS was higher, the quality of the oocytes was like that of non-PCOS patients [85]. Similarly, in 2015, Sigala, J. et al. compared the quality of oocytes in IVF between patients with PCOS and normal individuals. Despite the higher number of oocytes retrieved and embryos formed in PCOS patients within three days, the final percentage of top-quality embryos was similar between the two groups. These findings, along with several other

randomized controlled trials, have led to inconclusive results regarding the impact of PCOS on oocyte quality [86].

10. PCOS Management

Several studies demonstrated that using N-acetylcysteine (NAC), Myoinositol, d-chiro-inositol, and growth hormones in treating PCOS improved the quality of oocytes. A randomized prospective study was carried out on 60 Iranian women between the ages of 25-35 years who suffered from PCOS and were treated with intracytoplasmic sperm injection (ICSI). The women were divided into three groups based on whether they received NAC, Metformin, or both. The results of the study showed a decrease in Leptin levels in all groups, a reduction in Malondialdehyde levels in the groups given NAC, and a decrease in Insulin and Luteinizing Hormone (LH) levels in the groups given either NAC or Metformin alone. These changes improved oocyte maturation and quality, improved embryo development, and fewer immature oocytes. Therefore, NAC can be considered an alternative to Metformin for improving oocyte quality in PCOS patients [87].

Another study investigated the effect of Myo-inositol and folic acid on oocyte quality, which resulted in 70% restored ovulation and 15.1% pregnancies. No side effects were linked to the case. The follicle-to-retrieved oocyte ratio was significantly better after the treatment, with the quality of oocytes being higher than that of the placebo group. Moreover, the quantity of meta-phase I and II oocytes was higher, although not high enough to risk hyperstimulation syndrome [88]. Similarly, another study treated 14 patients with 4,000 mg of Myo-inositol and 400 µg folic acid daily for two months. This resulted in better oocyte quality, with 58.4% fertilization rate compared to 42.7% in the placebo group [29].

In a recent study, 50 infertile PCOS patients were divided into two groups, where both took 400 mg of folic acid. Still, only the experimental group was provided with 4 g Myo-inositol over the folic acid dose. The

time frame covered the period starting one month before the beginning of the antagonist cycle and ending on the day of ovum pickup. The oocyte and embryo quality was gauged according to the European Society of Human Reproduction and Embryology standards. Real-time PCR (RT-PCR) was used to analyze the phosphoglycerate kinase 1 (PGK1), the regulator of gene signaling 2 (RGS2), and cell division control protein 42 (CDC42) gene expressions to define the oocyte quality in granulosa cells. Comparable to previous studies, Metaphase II oocytes, embryo quality, and fertilization rates were greatly ameliorated in the group studied. The study also showed advanced gene expressions in the study group, while the quantity of retrieved oocytes and follicles was not significantly higher. Therefore, the above findings suggest that Myo-inositol enhances oocyte and embryo quality while affecting gene expressions in granulosa cells [89]. Earlier, Pacchiarotti et al. (2015) reviewed the consequence of mixing the treatment with Melatonin. Five hundred twenty-six random PCOS women were included in a randomized controlled trial and were divided into three categorical groups. The control group was given only folic acid, and two groups, A and B, were supplied with 4,000 mg of Myo-inositol. Group A differed from Group B by taking 3 mg of Melatonin. Overall, Group A proved that the mix resulted in a better quality for the oocyte and the embryo [90].

D-chiro-inositol can improve oocyte quality in a dose-dependent fashion. Based on a morphology assessment, any combination of Myo-inositol and d-chiro-inositol may improve the zona pellucida, plasma membrane, cytoplasm, and sperm reception by enhancing insulin sensitivity and reducing testosterone [91].

Growth Hormones (GH) can positively affect oocyte quality in PCOS patients. GH increases the serum levels of the total oxidant status and the OS index in the follicle fluid, which positively affects the oocyte quality [92]. Providing GH could improve IVF outcomes in patients with repeated IVF

cycles regarding oocyte number and quality [93].

11. Improvements Based on Treatments

It was shown that dehydroepiandrosterone (DHEA) treatment did not improve ovarian response and outcome when it comes to clinical pregnancy rate, number of retrieved oocytes, oocyte quality, and the rate of live birth following IVF in women with poor ovarian response [94]. To try to understand the effect of DHEA on IVF and its mechanism, granulosa cell expression was studied. However, there was no significant result when it came to up- or down-regulation in the group treated with DHEA as compared to the placebo group; therefore, DHEA did not have a considerable effect on a molecular level [95]. Other studies concerning DHEA treatment proved that exogenous androgen treatment (DHEA, transdermal testosterone) was beneficial and resulted in a reasonable clinical pregnancy rate and many embryos. FSH sensitivity in the growing and maturing follicles is promoted by intraovarian androgens [98, 99], improving oocyte yield and maturity and embryo quality, thus improving pregnancy rate. Therefore, to increase the concentration of intraovarian androgens, it was proposed to pretreat with DHEA or transdermal testosterone. [96, 97]

Molecular analysis was also conducted for expression of gonadotropins FSH and LH receptors, androgen receptors, oocyte developmental competence markers (such as PTX3, HAS2, PTGS2, and GREM1), as well as epidermal growth factors signaling molecules (such as EREG, AREG, and BTC) that showed and proved the clinical findings [94, 100].

On the other hand, hCG did not improve clinical outcomes when achieving pregnancy in patients categorized based on past failure to conceive or poor-quality embryos. To achieve ovulation induction, a lower dose of gonadotrophin was required. Cotreatment of clomiphene or letrozole with gonadotropin had the worst outcomes; thus, they should not be used for patients with POR. It is important to note that high FSH doses are

detrimental to oocyte quality, leading to a decrease in live births in subfertile patients, as well as chromosomally abnormal embryos of greater incidence [101]. These findings concerning GH supplementation were also supported by Yovich and Stanger (2010) who concluded that GH administered to IVF patients with gonadotropin-induced ovarian stimulation leads to improved oocyte quality by increasing FSH and LH receptor expression on granulosa cells [101, 102].

With GH supplementation, Growth Hormone Receptor [GHR] protein was expressed at higher levels by granulosa cells [79], which also increased oocyte mitochondrial function essential for the development of both oocyte and embryo. Thus, GH with ovarian stimulation regimens improves oocyte quality, possibly by an enhanced mitochondrial function and viability rather than mitochondria numbers [103]. Therefore, lower GHR expression and mitochondrial activity may contribute to decreased oocyte development associated with reproductive aging, supporting GH supplementation for clinical POR management.

Many studies showed that the quality of oocytes depends on appropriate metabolism and sufficient ATP. ATP synthesis requires carnitine. Wu et al. (2010) investigated if the regulation by carnitine would be beneficial for oocyte and embryo development but did not find any significant evidence that dietary carnitine would improve oocyte quality and fertility [28]. In vivo, dietary carnitine supplementation only has effects at the level of tissues when circulating levels are dysregulated [104].

An alternative to improve the pregnancy potential of deficient oocyte quantity and overall quality was described by Task Force Members et al. (2013), who reviewed the transfer of autologous mitochondria from ovarian cells, which could enhance oocyte performance. However, this treatment might not always be appropriate for women in advanced reproductive age because dysfunctional mitochondria are just one of many factors causing oocyte developmental

failure. High-quality mitochondria transferred from stimulated and naturally grown oocytes might strengthen and revitalize deficient oocytes, thus improving the quality and quantity of oocytes [105].

Patients with recurrent IVF failure, PCOS, Type II Diabetes, and other metabolic abnormalities have oocytes with mitochondrial malformations. [106–108]. Since the link between mitochondria and oocyte quality seems strong, as previously mentioned, the development of embryos and fertility might be directly affected by the mitochondrial quality and mtDNA. Increasing the number of mitochondria or improving their function by transferring them from high-quality oocytes would restore normal functionality. It is important to note that evaluating the active and healthy mitochondria before oocyte reconstruction is recommended and helpful for selecting all fertilizable oocytes [102]; proper methods for mitochondrial injection are also required to ensure enhanced fertility in low-quality oocyte patients.

Other studies indicated that human ovaries contained oogonial precursor cells (OPCs), which could be a source of healthy mitochondria. Lee et al. (2006) investigated whether OPC-derived autologous mitochondrial injection (AMI) would improve oocyte quality in women experiencing IVF failures. Higher fertilization rates and embryo grades post-AMI indicated improved oocyte quality [8].

For IVF-treated patients, another method to produce competent oocytes and embryos was suggested, especially in the case of urgent fertility preservation, like for cancer patients: Luteal Phase Ovarian Stimulation (LPOS) allows higher numbers of oocytes, improved oocyte quality, and better clinical outcomes after embryo transfer in POR patients [109].

In a study by Richter et al. (2005), Myoinositol was administered with Melatonin to 46 women who experienced failed conception in IVF cycles due to poor oocyte quality. The patients were then proceeded to new IVF cycles [110]. There was a

statistically significant post-treatment rise in the number of mature oocytes, fertilization rate, and total and top-quality embryos transferred compared to previous IVF cycles. In patients who were undergoing Intracytoplasmic Sperm Injection (ICSI), MI supplementation with Melatonin in the first three months before pickup of oocyte and Vitamin D3 capsules improved fertilization and pregnancy outcomes, reduced the risk of Ovarian Hyperstimulation Syndrome (OHSS) and improved oocyte and embryo quality as compared to the control group without treatment. These results were also seen when using Melatonin alone or combined with MI, especially when discussing oocyte retrieval and ICSI technique parameters; adding Vitamin D3 led to a higher pregnancy rate. Therefore, it was concluded that MI and melatonin administration before ICSI and MI, Melatonin, and Vitamin D3 administration after ICSI are useful to improve this IVF technique results and increase endometrial receptivity. Melatonin is a crucial factor in endometrium proliferation, while Vitamin D3, which has the same function as progesterone, supports the course of pregnancy.

A retrospective cross-sectional study demonstrated that administration of 20 mg of Duphaston orally per day from the third day of the cycle in IVF and ICSI cases can be used as a GnRH antagonist alternative for patients undergoing ovarian hyperstimulation and lead to successful outcomes. Given the lack of androgenic effects, Duphaston, like progesterone, is considered safe even at high doses [111]. This led to higher oocyte retrieval than GnRH antagonist administration while preventing early and premature LH surge. LH surge happens after activation, transmission, and GnRH surge [112], while progesterone blocks GnRH surge by preventing the premature surge of LH [113]. Progesterone can also block estradiol-induced LH surge in the early stages [114]. Therefore, the progesterone effects on LH surge depend on the administration time [115], thus using Duphaston to prevent premature LH surge in

IVF cases. Liu et al. (2017) investigated the improvement of egg quality by restoring a better and stronger oocyte maturation process, usually triggered by LH in vivo or hCG in IVF cases [114]. In this study, they found that putrescine (produced in peri-ovulatory ovaries for division regulation, differentiation, maturation, and apoptosis of cells) deficiency might cause poor egg quality, so supplementation of this biogenic polyamine reduces egg aneuploidy and miscarriage rates while improving embryo quality. These results were concluded based on mice studies. Yet, preliminary data concerning humans showed that Ovarian Ornithine Decarboxylase (ODC) deficiency is linked to maternal aging and is responsible for producing putrescine. [116], and can be used in IVF patients. Putrescine helps with ODC deficiency, targets the maturation of oocytes in a brief amount of time (unlike CoQ10 and others) [116], and can be used in IVF patients and natural conception.

It improves live birth rates in older women because of its ubiquitous nature and chemical stability/clearance, improving embryo quality significantly [81].

12. Strengths and Limitations

To our knowledge, this is the most comprehensive narrative review on this topic. We were able to combine data from 118 articles and summarize them. This article would serve as an essential educational tool for specialty physicians. However, this review has a few limitations to take into consideration. First, this narrative review does not present any new information. It is just a summary of what the literature reported. The study was limited to two search terms, "Oocyte Quality" and "IVF cycle," and was not more focused. We searched specific databases, which may have limited the scope of the review.

Table 1: Summary of Factors Affecting Oocyte Quality and their Pathophysiology

Factors Affecting Oocyte Quality	Pathophysiology
Age	<ul style="list-style-type: none"> - Less qualified cytoplasm - High rate of genomic abnormalities - Chromosomal and mitochondrial abnormalities - Shorter telomeres - Decrease in DNA repair
Obesity	<ul style="list-style-type: none"> - High oxidative stress state, hence, rise in ER stress
Endometriosis	<ul style="list-style-type: none"> - Anatomical abnormalities - Increase in cortical granule loss and zona pellucida thickening, affecting fertilization - Decrease in germinal vesicles reaching Meiosis II - Oocyte dysmorphism - Mitochondrial abnormalities - High levels of ROS and pro-inflammatory cytokines
Cyclic Nucleotides	<ul style="list-style-type: none"> - Increase in pre-implantation embryo development and overall quality
Thalassemia	<ul style="list-style-type: none"> - Decrease ovarian reserve - Iron overload due to repeated blood transfusion affecting ovarian reserve directly by redox activity in oocyte follicular fluid
Malignancies	<ul style="list-style-type: none"> - Premature ovarian insufficiency and infertility due to anti-neoplastic drugs
PCOS	<ul style="list-style-type: none"> - Chronic inflammatory state unfavorable for folliculogenesis - Intrinsic intrafollicular abnormalities - Increased levels of palmitoleic acid and oleic acid in PCOS patients without obesity, correlated with oocyte developmental competencies - Increase in OS

Conclusion

In conclusion, due to the rising number of subfertility cases, the role of ART is getting more important daily. IVF success rates depend highly on oocyte quality and level of maturation. Several factors affect these two entities: obesity by increasing O₂ and H₂O₂ resulting in a rise of ER stress state, PCOS, age, endometriosis, cyclic nucleotides used in IVF, thalassemia major by having a lower ovarian reserve and increased level of redox activity, malignancies, and anti-neoplastic drugs being a potential cause of premature ovarian insufficiency. Many treatment options have been proposed to improve oocyte quality and level of maturation, including GH supplementation with ovarian supplementation, transfer of autologous mitochondria, luteal phase ovarian stimulation, MI-Melatonin-Vitamin D3 administration, Duphaston and Putrescine supplementation. Dehydroepiandrosterone, hCG, and Clomiphene or Letrozole-Gonadotropin treatment did not significantly improve ovarian response and outcome regarding oocyte quality.

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