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Oocyte Aging: The Role of Cellular and Environmental Factors and Impact on Female Fertility

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Abstract

Female aging is one of the most important factors that impacts human reproduction. With aging, there is a natural decline in female fertility. The decrease in fertility is slow and steady in women aged 30–35 years; however, this decline is accelerated after the age of 35 due to decreases in the ovarian reserve and oocyte quality. Human oocyte aging is affected by different environmental factors, such as dietary habits and lifestyle. The ovarian microenvironment contributes to oocyte aging and longevity. The immediate oocyte microenvironment consists of the surrounding cells. Crosstalk between the oocyte and microenvironment is mediated by direct contact with surrounding cells, the extracellular matrix, and signalling molecules, including hormones, growth factors, and metabolic products. In this review, we highlight the different microenvironmental factors that accelerate human oocyte aging and decrease oocyte function. The ovarian microenvironment and the stress that is induced by environmental pollutants and a poor diet, along with other factors, impact oocyte quality and function and contribute to accelerated oocyte aging and diseases of infertility.

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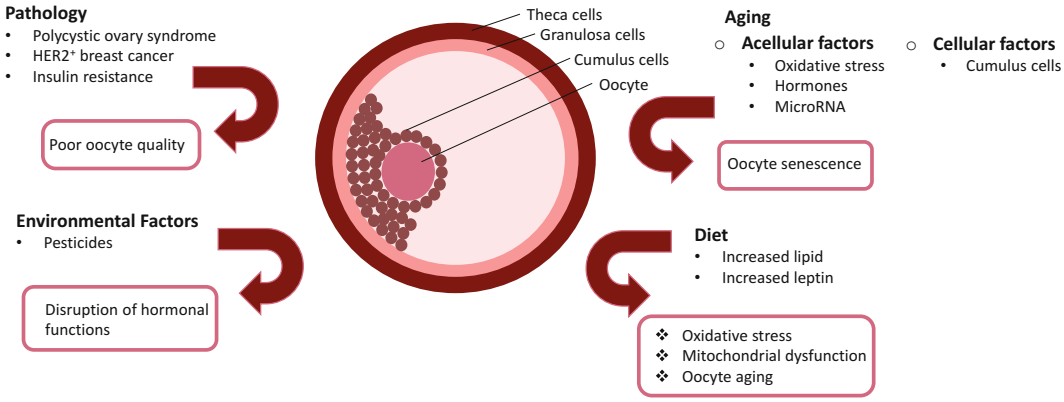
Graphical Abstract



Keywords

Aging and longevity · Human · Microenvironment · Oocytes

Abbreviations

AGEs	Advanced glycation end products
AKT	Protein kinase B
BCL2	B-cell lymphoma-2
CaMKII	Calmodulin-dependent protein kinase II
CAT	Catalase
CCs	Cumulus cells
cGMP	Cyclic guanosine monophosphate
COC	Cumulus-oocyte complex
COIII	Cytochrome oxidase subunit 3
CoQ10	Coenzyme Q10
Cx-43	Connexin 43
EGF	Epidermal growth factor
EGFR	EGF receptor
FADD	Fas-Associated protein with a Death Domain
FAS	Free α-subunit
FasL	Fas/Fas ligand
FoxO	Forkhead box O
FSH	Follicle-stimulating hormone
GCs	Granulosa cells
GnRH	Gonadotropin-releasing hormone
GSSPx	Glutathione peroxidase
GST	Glutathione S transferase
GTP	Guanosine triphosphate
HMGA2	High-mobility group AT-hook 2
HPG axis	Hypothalamic-pituitary-gonadal axis
IKBKG	Inhibitor nuclear factor kappa B kinase subunit gamma
IR	Insulin resistance
IVF	In vitro fertilization
LH	Luteinising hormone
LINE-1	Long interspersed element
MAPKs	Mitogen-activated protein kinases
MII	Meiotic metaphase II
MnSOD	Mitochondrial SOD
MPF	Maturation-promoting factor
mtDNA	Mitochondrial DNA
NAC	N-acetyl-L-cysteine
NAD+	Nicotinamide adenine dinucleotide
NF-κB	Nuclear factor kappa B
ORFs	Open reading frame
PCOS	Polycystic ovary syndrome
PDE3A	Phosphodiesterase 3A
PGC-1 α	Proliferator-activated receptor coactivator-1α
PGCs	Primordial germ cells
PI3K	Phosphatidylinositol 3-kinase
PTEN	Phosphatase and tensin homolog
RAB5B	Ras-related protein Rab-5B

RAGE	Receptor for advanced glycation end products
ROS	Reactive oxygen species
SDHA	Subunit A of succinate dehydrogenase
sFasL	Soluble fasl
SIRT1	Silent information regulator-1
SOD1	Superoxide dismutase

1 Introduction

The development of oocytes from primordial germ cells (PGCs) is a tightly regulated process. The female fetal ovary begins to display follicular atresia as early as 28 weeks of gestation, and follicular atresia continues throughout adult life. Of the one to two million oocytes in the ovary of a new-born baby, only 300–400 oocytes reach the ovulation stage (Oktem and Oktay 2008). After ovulation, mammalian oocytes are arrested at the meiotic metaphase II (MII) stage. If not fertilized in time, the ovulated oocytes undergo a time-dependent aging process (Yanagimachi and Chang 1961; Whittingham and Siracusa 1978). Aged oocytes are associated with a significant reduction in embryonic development and maturation, especially following *in vitro* fertilization (Whittingham and Siracusa 1978; Iwamoto et al. 2005; Wu et al. 2007). The factors that impact oocyte longevity and aging are poorly understood. Why oocytes age and how the surrounding cells keep them alive while contributing to their aging is a fundamental biological question that requires substantial research. In this review, we identify the microenvironmental factors that contribute to oocyte aging and impair their fecundity. Identifying these factors and the underlying mechanisms of oocyte sustenance is fundamental to understanding oocyte biology and embryological development and could provide new insight into assisted reproductive technology.

2 Oocyte Development and Maturation

2.1 Structure

Ovarian tissue consists of two compartments: the cortex and the medulla. The medulla is the central compartment and is composed of connective tissue, fibrous tissue, and blood vessels. The cortex is the peripheral compartment and contains ovarian follicles at different stages of maturation. Each follicle consists of an oocyte surrounded by a layer of follicular cells. As the oocyte matures, additional layers of follicular cells are formed, and the cells in these layers are called granulosa cells (Grabowski and Tortora 2000).

2.2 Oogenesis

At 7 weeks of gestation, oogenesis begins in the female embryo from PGCs. At 20 weeks of gestation, each fetal oogonium in the ovary becomes a primary oocyte and remains arrested in prophase I of meiosis until puberty (Oktem and Oktay 2008; Oktem and Urman 2010; Mamsen et al. 2011). At 28 weeks of gestation, follicular atresia begins, and thus, there are only one million oocytes present in the ovary at birth (Oktem and Oktay 2008). Atresia continues throughout adult life so that only 300–400 oocytes reach the ovulation stage (Oktem and Oktay 2008). Directly before ovulation, luteinising hormone (LH) induces the continuation of the first meiotic division of the oocyte, resulting in two cells: the secondary oocyte, which is large and has most of the cytoplasm, and the polar body, which is small (de Haan et al. 2010). The secondary oocyte continues meiosis II and becomes arrested in the metaphase stage, which is completed after fertilization (de Haan et al. 2010).

2.3 Folliculogenesis

Starting from 15 weeks of gestation, the primordial follicles develop and mature within the ovaries until the oocyte reaches prophase I (Gougeon 1986). Primordial follicles mature to become primary, secondary, pre-antral, antral, and then pre-ovulatory "Graafian" follicles (Gougeon 1986). This process is known as folliculogenesis. At puberty, gonadotropins secreted by the pituitary gland promote the development of a set of antral follicles into Graafian follicles. Follicle-stimulating hormone (FSH) is produced during the early stage of antral follicle maturation, while both FSH and LH are produced during the late stage. Under the influence of these hormones, the follicles enlarge and develop their antra that contain the follicular fluid (Gougeon 1986). One of these sets of selected follicles becomes dominant, and the rest undergo follicular atresia (Johnson and Everitt 2000).

3 Risk Factors Affecting Oocyte Longevity

3.1 Aging

3.1.1 Cumulus Cells and Aging

Cumulus cells (CCs) are functional cells that originate from undifferentiated granulosa cells (GCs). CCs have highly specialized cytoplasmic projections that pass through the zona pellucida to form gap junctions with the oocyte and surround them to form the cumulus-oocyte complex (COC) (Albertini et al. 2001). The COC has a vital role in the development of healthy embryos since it provides the essential nutrients for oocyte maturation through different paracrine signalling pathways (Mehlmann 2005). Moreover, after ovulation, CCs remain loosely attached to the oocytes to support their journey to be released from the ovary.

Animal studies have shown the importance of CCs in the maturation of rodent oocytes *in vitro*. Oocytes co-cultured with CCs are able to produce a healthy mature foetus, whereas the absence of CCs in *ex vivo* culture conditions leads to a low success rate for oocyte maturation (Vanderhyden and Armstrong 1989). CCs play a dynamic role in regulating the process of oocyte aging and longevity (Perez et al. 2005) through many pathways, most notably the activation of Fas/Fas ligand (FasL) (Ju et al. 1995; Dhein et al. 1995; Matsumura et al. 1998; Poulaki et al. 2001) and the production of ceramide (Kujjo and Perez 2012).

Fas/FasL Pathway

CCs contribute to oocyte aging via activation of the Fas/FasL pathway, a major pathway involved in inducing the death of different cell types (Ju et al. 1995; Dhein et al. 1995; Matsumura et al. 1998; Poulaki et al. 2001). Mediated by metalloproteinases, FasL cleavage releases the soluble form of FasL (sFasL) (Kayagaki et al. 1995; Tanaka et al. 1995; Mitsiades et al. 1998). sFasL increases reactive oxygen species (ROS) levels through an NADPH oxidase-dependent mechanism. This increase in ROS activates Fas in the oocytes, which in turn activates the cytochrome c and phospholipase C-γ pathway and triggers Ca^{2+} secretion from the cytoplasmic reticulum. This Ca^{2+} release in turn activates caspase-3 and calcium/calmodulin-dependent protein kinase II (CaMKII). Activated caspase-3 accelerates further Ca^{2+} production, leading to the activation of more caspase-3 and to oocyte fragmentation (Zhu et al. 2016). Activated CaMKII inactivates maturation-promoting factor (MPF) and causes cyclin B degradation, resulting in increased oocyte susceptibility to apoptosis. Alternatively, upon the binding of FasL to Fas, Fas-Associated protein with a Death Domain (FADD) activates caspase-8, activating apoptosis (Itoh et al. 1991).

Aging oocytes have been found to be surrounded by CCs that secrete sFasL. sFasL secretion is thus believed to be the mechanism by which CCs accelerate oocyte aging and decrease oocyte development and maturation potential (Zhu et al. 2015a). This hypothesis is supported by the finding of the lack of oocyte aging when functional FasL is not present (Zhu et al. 2015b).

The expression of the FasL inhibitor B-cell lymphoma-2 (BCL2) is significantly upregulated in CCs associated with mature oocytes but not in those associated with immature oocytes (Filali et al. 2009). This suggests that BCL2 expression is strongly related to oocyte quality and potential for maturation; however, the mechanism of this association has yet to be investigated.

Ceramide Level and Mitochondrial Activity

When oocytes isolated from aged female mice were cultured with their surrounding CCs, there was a dramatic increase in the oocyte death rate compared to oocytes isolated from young mice (Fujino et al. 1996). Subsequent experiments showed that this age-related oocyte death rate was highly dependent on the presence of oocyte-surrounding CCs, as oocytes harvested from aged females and cultured without their surrounding CCs did not exhibit this high death rate (Perez and Tilly 1997). These experiments confirmed the postulation that CC-derived factor(s) are transported into the oocyte and activate the death programme in aged oocytes (Perez and Tilly 1997). Chemicals such as ceramide, a bioactive lipid produced by CCs and transported into oocytes, could be responsible for enhancing the age-related elevation in oocyte apoptosis (Perez et al. 2005; Kujjo and Perez 2012). Ceramide is translocated from CCs into their neighbouring oocyte via gap junctions, and its release induces apoptosis. This study showed that during aging, apoptosis is accelerated in female oocytes and that this process requires regular oocyte-CC communication. The higher apoptotic rate of the aged oocytes was correlated with higher oocyte sensitivity to increased cytosolic ceramide levels and overexpression of both bax mRNA and Bax protein. Other experimental studies have shown that during aging, the ceramide content of mitochondria decreases, resulting in subsequent structural and functional mitochondrial alterations and effects on oocyte quality (Kujjo and Perez 2012).

During early embryogenesis, mitochondria are the most prominent oocyte organelles, and the mitochondria of the embryo are almost exclusively derived from oocytes (Dumollard et al. 2007; Eichenlaub-Ritter et al. 2011; Van Blerkom 2004, 2011; Van Blerkom et al. 2006). Because of their essential role in cellular energy production and the regulation of cell death, mitochondria control the life and death decisions of most cell types, including oocytes (Danial and Korsmeyer 2004; Perez et al. 2000; Wang 2001). Furthermore, mitochondria are responsible for chromosome segregation and normal spindle formation (Eichenlaub-Ritter et al. 2004). Because of their small sizes and simple internal structures, oocyte mitochondria have been described as morphologically primitive or immature (Dumollard et al. 2007). However, mitochondrial dysfunction is involved in general body aging, (Ames et al. 1995; Sastre et al. 2002) as well as the aging of female reproductive tissues (Ruman et al. 2003; Gougeon 2005; Janny and Menezo 1996; Ottolenghi 2004; Tarlatzis and Zepiridis 2003; Kirkwood 1998). During aging, disruptions in intracellular ceramide synthesis and transport cause abnormal mitochondrial ceramide levels. This ceramide imbalance negatively impacts the functionality of the oocyte mitochondria and the oocyte quality.

3.1.2 Oxidative Stress and Aging

Oxidative stress is considered one of the most critical mechanisms underlying cellular aging (Tatone et al. 2008a; Salmon et al. 2010). Oxidative stress occurs when the production of ROS and the scavenging effects of antioxidants become imbalanced. This imbalance results in the accumulation of ROS that are produced during normal metabolism. Oxidative stress in the ovary leads to follicular atresia and to a reduction in the number and quality of oocytes (Tatone et al. 2008a). This accounts for defects in oocyte maturation and fertilization and for age-associated decreases in fertility (Agarwal et al. 2005). Oxidative stress also enhances telomere shortening and chromosomal segregation disorders, resulting in defects in meiosis, fertilization, embryo development and, ultimately, infertility (Richter and von Zglinicki 2007).

Aging is associated with increased levels of ovarian advanced glycation end products (AGEs), which are responsible for the generation of

increased levels of ROS (Tatone et al. 2008b; Yin et al. 2012). This is mediated by binding to certain receptors called receptor for advanced glycation end products (RAGE) that induce the activation of NAD(P)H oxidase, mitogen-activated protein kinases (MAPKs), and the transcription factor nuclear factor kappa B (NF-κB) (Lander et al. 1997; Brownlee 2001). The follicular fluid of older cows has been reported to have higher levels of AGEs than that of their younger counterparts (Takeo et al. 2017). Higher levels of AGEs in older cows are associated with fertilization defects. Another study shows that the expression of AGE precursor, detoxifying methylglyoxal, is reduced in older female mice compared to their younger counterparts (Tatone et al. 2010). These data reflect the important role of AGEs in ROS production in older ovarian tissue (Tatone et al. 2008b).

The mature oocyte is a large cell with a high number of mitochondria and large amounts of mtDNA (Monnot et al. 2013). Oocytes can be inactive for years, and during this period, they are continually exposed to oxidative stress leading to mitochondrial DNA (mtDNA) mutations (Kitagawa et al. 1993). Moreover, since ovarian tissues undergo slow turnover, mitochondrial-related defects are highly expected. In the oocytes of older women, there is a high risk of a 4977-bp deletion that affects a subset of genes involved in mitochondrial function and the activity of its enzymes, such as ATP synthases 6 and 8, cytochrome oxidase subunit 3 (COIII), and NADH (Fragouli and Wells 2015). Additionally, the mtDNA quantity of older women suffering from diminished ovarian reserve is higher than that of younger women with normal ovarian reserve (Boucret et al. 2015). There seems to be a difference between older and younger oocytes regarding mitochondrial function and the expression of oxidative stress genes (Hamatani et al. 2004). For example, subunit A of succinate dehydrogenase (SDHA), which is involved in energy-generating pathways, is highly expressed in younger oocytes (Hamatani et al. 2004). This may explain the decrease in ATP production in older oocytes. Additionally, oxidative stress-related genes such as superoxide dismutase (Sod1) and thioredoxin family (Txn1 and Apacd) are downregulated in older oocytes (Hamatani et al. 2004), and the heat shock response and ubiquitin–proteasome pathway are inhibited (Matsui et al. 1996). This leads to the accumulation of damaged proteins, decreased expression of Hsp7 family genes (Hspa4, Hspa8 and Hsp70), and decreased expression of heat shock genes of the ubiquitin–proteasome pathway, such as Hip2, Ubc, Ube1c, Ube2a, Ube2e3, Ube2g1, Pama6, Pamb1, Psmb4, Psmc2, Psmc3, Psmd12, Siah2 and Anapc4, in older oocytes (Hamatani et al. 2004).

Furthermore, there is structural damage in the mitochondria of GCs of older oocytes that is similar to that of oocytes exposed to hypoxia (Amicarelli et al. 1999). This may be explained by the oxidative stress caused by the inadequate blood supply to the theca of mature follicles and the increases in metabolism and oxygen demand by the mature oocyte.

Antioxidants that are present in the follicular fluid, such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSSPx), have ROS scavenging actions and protect oocytes against ROS-mediated damage (Carbone et al. 2003). Glutathione S transferase (GST) also acts as a detoxifying agent against ROS by products. This antioxidant defence is greatly affected by ovarian aging.

In older women, the levels of GST and CAT in the follicular fluid decrease (Carbone et al. 2003). The CAT/SOD ratio and GSSPx/SOD ratio in the follicular fluid also decrease, reflecting the decrease in ROS scavenging efficiency with aging (Carbone et al. 2003). This is accompanied by downregulation of the activity of antioxidants, namely, the Cu/Zn SOD, MnSOD, and CAT genes in GCs. The roles of these antioxidants are to scavenge the superoxide anions and hydrogen peroxide released during the synthesis of steroid hormones.

As nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylases (Morris 2013; Calabrese et al. 2010), sirtuins control the acetylation of histone and non-histone factors, (Huang et al. 2007) thereby controlling the process of aging. For instance, silent information regulator-1 (SIRT1) catalyses the de-acetylation

of the forkhead box O (FoxO) gene promotor, which is critical for the cellular stress response (Brunet et al. 2004). This in turn upregulates key antioxidant enzymes, such as CAT, mitochondrial SOD (MnSOD), and peroxiredoxin, thereby regulating the cellular redox status (He et al. 2010; Kao et al. 2010; Hasegawa et al. 2008; Hori et al. 2013). Additionally, SIRT1 deacetylates the promoter region of the proliferator-activated receptor coactivator-1α (PGC-1α), enhancing its expression. PGC-1α activates genes involved in antioxidative protection (such as glutathione peroxidase, CAT, and MnSOD), mitochondrial biogenesis and metabolic function (Nemoto et al. 2005; Liang and Ward 2006; Gerhart-Hines et al. 2007). Moreover, SIRT1 inhibits nuclear factor β (NF-B), which is a critical inducer of the inflammatory response mediated by oxidative stress. This, in turn, decreases ROS levels and inflammation (Yeung et al. 2004; Kauppinen et al. 2013). However, the levels of SIRT3, a critical regulator of mitochondrial function, decrease with the age of CCs and GCs. This consequently impairs follicular metabolism (Lombard et al. 2011; Pacella-Ince et al. 2014) and decreases the generation of certain hormones, such as progesterone, in gonadal cells (Li et al. 2017).

3.1.3 MicroRNAs and Oocyte Aging

Maternal age is associated with the compromised function of CCs (Tatone and Amicarelli 2013), resulting in epigenetic modifications and altered miRNA functions in aged oocytes (Ge et al. 2015). miRNAs are small noncoding RNAs that bind to target messenger RNAs (mRNAs) to inhibit their expression. mRNAs exist either freely or enclosed in vesicles (exosomes) in the human follicular fluid to enable CCs and the adjacent oocytes to regulate oocyte DNA methylation (da Silveira et al. 2012; Sang et al. 2013a; Assou et al. 2013).

Aging affects the follicular environment, including its protein composition (Pacella et al. 2012; McReynolds et al. 2012). Since miRNAs are responsible for the regulation of protein expression, experimental studies show a correlation between their function and aging oocytes. Aging is associated with increased levels **of miR-190b**, which targets Exostosin-1 (EXT1). EXT1 is a glycosyltransferase that is required for the biosynthesis of heparan sulfate, which regulates the pattern and intensity of the response to oocytes during COC expansion and oocyte maturation (Watson et al. 2012). Via this mechanism, miR-190b contributes to the deregulation of follicle morphogenesis and abnormal glucose metabolism in the follicles of older women (Pacella et al. 2012).

Aging is also associated with decreased levels of **miR-21-5p**; miR-21-5p targets several genes that are important in the p53 pathway, which plays a crucial role in the aging process (Collado et al. 2007). Moreover, higher levels of **miR-134** are observed in older women, which indicates decreased expression of BCL2 and inhibition of the apoptosis inhibitor nuclear factor kappa B kinase subunit gamma (IKBKG). Aged oocytes have lower expression of **miR-132**, which inhibits Sirtuin-1 (SIRT1) expression. This is achieved through increased antioxidant superoxide dismutase 2 (sod2) gene expression and a concomitant decrease in intracellular ROS in response to oxidative stress.

3.1.4 Hormonal Control and Aging

There are differences in the transcriptome profiles of the oocytes of young and older women (Grøndahl et al. 2010). The functions of gonadotropin-releasing hormone (GnRH), FSH, and LH are compromised by the aging process (Santoro et al. 1998). GnRH is a master hormone that is secreted by the hypothalamus and regulates the release of gonadotropins (FSH and LH) from the anterior pituitary gland. LH stimulates theca cells to produce androstenedione, while FSH stimulates the conversion of the theca-derived androstenedione into oestradiol, in addition to the synthesis of inhibin, by the GCs in the small antral follicles (Barbieri 2014). Under physiological conditions, a negative feedback loop of gonadotropin secretion is triggered by gonadal inhibin to allow appropriate follicle growth and development (Luisi et al. 2005).

In animal models, disruption of the hypothalamic-pituitary regulatory axis is

associated with reproductive aging (Wise et al. 1997). It was demonstrated that destabilization of the neuroendocrine signals by the aged brain is responsible for the accelerated rate of follicular loss and early menopausal transition (Wise et al. 1997). When FSH receptors in female mice are knocked out at different ages, haplo-insufficiency (−/+) of FSH receptors in seven-month-old females is associated with accelerated oocyte death. Interestingly, none of the one-year-old (+/−) females produced viable offspring (Danilovich and Sairam 2002).

In humans, the effect of aging on the hypothalamic-pituitary reproductive axis is more controversial. The depletion of the follicle number at menopause leads to cessation of negative feedback inhibition and increased levels of serum FSH and LH (MacNaughton et al. 1992). However, other studies have demonstrated a decline in gonadotropin levels, especially LH, in postmenopausal women, most likely due to changes in hypothalamic GnRH stimulation (Scaglia et al. 1976). These findings are supported by another study, in which a dynamic correlation between aging and a decline in the GnRH pulse was frequently observed and in which this correlation was independent of gonadal feedback (Hall et al. 2000). Reduced levels of serum gonadotropin free α-subunit (FAS) and LH, as neuroendocrine markers of plausible GnRH secretion, were reported in a group of postmenopausal women compared with their younger peers. These results confirmed the role of aging in hypothalamus function, and while this role is independent of gonadal function, it may represent an impetus for reproductive senescence (Hall et al. 2000).

3.2 Diet

3.2.1 The Role of Oxidative Stress

Antioxidants play a critical role in maintaining ovarian function and fertility (Lim and Luderer 2011). Supplementation of antioxidants decreases ROS-mediated oocyte damage and preserves the quality of aging oocytes and follicles. This was shown *in vitro* following the application of antioxidant *N*-acetyl-L-cysteine (NAC) to oocyte culture (Liu et al. 2012). The underlying mechanism was shown to be mediated by a reduction in telomere shortening, telomere fusion, DNA damage and chromosomal instability in oocytes. Long-term melatonin treatment ameliorates ovarian mitochondrial oxidative damage (Song et al. 2016). This protection of the ovarian tissue from aging is achieved by decreasing mitochondrial ROS generation, inhibiting apoptosis, suppressing the collapse of mitochondrial membrane potential and maintaining respiratory chain complex activities. Notably, melatonin is an endogenously generated indoleamine that plays a significant role in preventing the aging-related impairment of redox status through its antioxidants and ROS scavenging actions (Manda et al. 2007). Melatonin administration and vitamin E treatment thus lead to the improvement of the fertilization rate in patients undergoing *in vitro* fertilization (IVF) and embryo transfer (Tamura et al. 2008).

Decreased caloric intake has been shown to be associated with decreases in oocyte ROS in older females (Barja 2002, 2004). Caloric restriction for more than 6 months in 12-month-old mice resulted in reduced aneuploidy, meiotic spindle defects, and mitochondrial dysfunction compared to non-calorie-restricted controls (Selesniemi et al. 2011). This was explained by the decreased expression of proliferator-activated receptor γ coactivator-1α (PGC-1α), a critical regulator of mitochondrial respiration. Thus, caloric restriction may preserve oocyte quality in older females. The levels of coenzyme Q10 (CoQ_{10}) production, an important regulator of the electron transport chain, were shown to be reduced in aged oocytes. This was associated with decreased ATP production and increased spindle abnormities, leading to infertility (Ben-Meir et al. 2015).

3.2.2 Diet and Hormonal Control

As obesity is an evolving worldwide epidemic according the WHO report (Organization, W.H and W.H.O.M.o.S.A. Unit 2014), weight control has become an important contributing factor to preserving fertility. Obese women have difficulty conceiving, even at a younger age (Jensen et al. 1999). Obesity is associated with anovulation,

polycystic ovarian syndrome and pregnancy complications, such as miscarriage, gestational diabetes, preeclampsia, (Jungheim and Moley 2010) and poor IVF outcomes (Shah et al. 2011). However, limited research is available on the underlying pathophysiological mechanisms of many of these complications. Recent studies related obesity to alterations in the ovarian follicular microenvironment (Robker et al. 2009; Metwally et al. 2007). Intra-follicular insulin, triglyceride and lipoprotein receptors, as well as inflammatory markers such as C reactive protein, were shown to be significantly elevated in obese women compared to women of normal weight (Robker et al. 2009). Furthermore, high leptin levels have been reported in the blood and follicular fluid of obese women (Metwally et al. 2007). Leptin is an adipocyte-derived hormone that has a stimulatory effect on the hypothalamic-pituitary-gonadal axis (HPG axis), in addition to its role in energy homeostasis (Garcia-Galiano et al. 2014). During leptin resistance, excess leptin inhibits insulin-induced ovarian steroidogenesis by acting on the receptors of theca and GCs. Furthermore, Leptin inhibits LH-stimulated oestradiol production by GCs (Moschos et al. 2002). The reproduction rate of female rats that have dietary-induced obesity and hyperleptinaemia is decreased by 60% (Tortoriello et al. 2004). In humans, hyperlipidaemia in obese women leads to oxidative stress in the endoplasmic reticulum as well as to the production of ROS, resulting in mitochondrial dysfunctions and aging (Robker et al. 2011).

3.3 Diseases Associated with Oocyte Aging

3.3.1 Polycystic Ovary Syndrome (PCOS)

PCOS is a common endocrine disorder that is frequently encountered in women during their reproductive years (Trikudanathan 2015). It has heterogeneous phenotypic characteristics that include oligo-ovulation or anovulation, clinical and/or biochemical signs of hyper-androgenism, polycystic ovaries, metabolic syndrome, and infertility (Trikudanathan 2015). Hypermethylation of long interspersed element (LINE-1) DNA in CCs correlates with oocyte maturation and PCOS pathophysiology. LINEs are a group of genetic elements that produce RNA and that transcribe in the antisense direction of pre-mRNA. Thus, LINEs limit mRNA levels and control the expression of genes containing LINE regulatory sequences (Sukapan et al. 2014; Yooyongsatit et al. 2015; Wanichnopparat et al. 2013; Aporntewan et al. 2011). LINE-1 has two open reading frames (ORFs) that encode ORF1P and ORF2P, which are essential proteins for its re-integration into the genome. ORF1P is implicated in oocyte meiotic maturation. Hypermethylation of LINE-1 decreases ORF1P expression, which in turn decreases CDC2 and CYCLINB1, which are components of maturation-promoting factors. These factors are regulators of the G2/M transition (Stanford et al. 2003). Additionally, the decrease in ORF1P triggers and upregulates γH2AX, an indicator of the DNA damage response.

miRNA Expression and PCOS

PCOS is associated with decreases in the expression of miRNA-132 and -320 in the follicular fluid. miRNA-132 downregulates the phosphatase and tensin homolog (PTEN) gene (Santonocito et al. 2014), which in turn activates protein kinase B (AKT) and switches on the phosphatidylinositol 3-kinase (PI3K) signalling pathway. This pathway is involved in follicular maturation. Additionally, miRNA-132 and miRNA-320 target the expression of candidate PCOS genes, namely, high-mobility group AT-hook 2 (HMGA2) and Ras-related protein Rab-5B (RAB5B) (Sang et al. 2013b). This sheds light on the role of miRNAs in the aetiology of PCOS.

A reduction in miR-29a-3p is also evident in follicular fluid from PCOS patients. This microRNA targets PTEN (Tumaneng et al. 2012), thereby causing increased cell growth. The decreased expression of miR-29a-3p is thus accompanied by arrested follicle growth and follicular development in PCOS patients (Sørensen et al. 2016). Furthermore, PCOS is accompanied by increases in miR-224, miR-378, and miR-383 expression (Sang et al. 2013b). These miRNAs

regulate aromatase expression during follicle development (Yin et al. 2012; Zhao et al. 2011; Xu et al. 2011). Along with follicular cell activity, aromatase expression is a hallmark of PCOS.

3.3.2 HER2$^+$ Breast Cancer

HER2$^+$ breast cancer is associated with the overexpression of epidermal growth factor (EGF) (Lee et al. 2015). Upon the binding of EGF to EGF receptor (EGFR), Ras (a small GTPase) swaps its GDP for a GTP molecule and becomes activated. Activated Ras activates MAPKs. This pathway is known as the Ras-MAPK pathway. This leads to the phosphorylation of the gap junction protein Connexin 43 (Cx-43) and a decrease in gap junction permeability, resulting in reduced NPR2 activity. NPR2 is a guanylate cyclase that catalyses the conversion of intracellular guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). Reduced cGMP in oocytes activates phosphodiesterase 3A, cGMP-inhibited (PDE3A), which in turn degrades cAMP and leads to meiosis resumption. Specific miRNAs have been shown to function within these pathways and regulate the processes of follicular development and meiotic resumption. The mRNAs that regulate these processes include miR-29a, miR-99a, miR-100, miR-132, miR-212, miR-214, miR-218, miR-508-3p, and miR-654-3p, which are upregulated in follicular fluid compared to plasma.

3.3.3 Insulin Resistance

Insulin is an evolutionarily conserved protein hormone that regulates diverse biological functions such as glucose homeostasis, cellular growth, aging, fertility and reproduction (Sliwowska et al. 2014; Tatar et al. 2003). Many studies have demonstrated the gonadotropic action of insulin on the ovary via specific signalling pathways that interact with FSH and LH during oogenesis and folliculogenesis (Sliwowska et al. 2014; Dupont and Scaramuzzi 2016). Moreover, insulin has been used as a supplement for *in vitro* culture at the early stage of human follicles. It was reported that insulin plays a survival role whereby the number of atretic follicles decreases and the number of healthy viable oocytes increases in culture (Louhio et al. 2000).

Insulin resistance (IR) and the resulting hyperinsulinaemia are well-recognized characteristics of polycystic ovary syndrome (PCOS) that lead to ovulatory dysfunction and infertility in women (Dale et al. 1998). Infertility has been attributed to hyperinsulinaemia, which suppresses sex hormone-binding globulin synthesis in the liver, rather than to peripheral IR (Nestler 1997). Sex hormone-binding globulin is a glycoprotein composed of two 373-amino-acid subunits that transport sex steroids, such as testosterone, to target tissues (Wallace et al. 2013). Hyperinsulinaemia thus promotes high levels of free testosterone in obese women with PCOS, remarkably affecting oocyte quality (Nestler 1997).

In female mice, IR has been found to stimulate oxidative phosphorylation in the mitochondria, where ROS is formed and antagonized by antioxidants (Boirie 2003). However, in IR, an imbalance between oxidants and antioxidants is observed and results in impaired mitochondrial function in the germinal vesicle and MII oocytes of insulin-resistant mice. A previous report indicated that apoptosis of germinal vesicle oocytes occurred at an early stage and that atretic and poor-quality MII oocytes were obtained from these mice.

3.4 Environmental Pollutants and Oocyte Aging

Pesticides and Oocyte Aging

The exposure of women to pesticides on a daily basis and a lack of precautions is considered an important occult cause of fertility problems. Pesticides of different types and variable levels of toxicity have been shown to interfere with female sex hormones and cause dysregulation of the ovarian cycle (Farr et al. 2004). The exposure of women to pesticides occurs in daily life in the form of consuming pesticide-laced fruits and vegetables and contaminated drinking water, the use of household and gardening supplies, and the

use of some cosmetic and cleaning substances, such as dog shampoos. Pesticide-induced disruption of hormonal functions in women has been shown to be associated with disruptions in the menstrual cycle, fertility reduction, conception failure, stillbirths, spontaneous abortions, and developmental defects (Schettler et al. 1997; Razi et al. 2016; Bretveld et al. 2006). Pesticides, such as lindane, atrazine and mancozeb, have toxic hormonal properties, leading to delayed ovulation and menstrual cycle disruptions in animal models (Chadwick et al. 1988; Ashby et al. 2002; van Birgelen et al. 1999). Atrazine was specifically shown to decrease LH concentrations, leading to anovulation (Ashby et al. 2002). Another pesticide, polychlorinated biphenyl 126, has been shown to be associated with alterations in oocyte and blastocyst maturation and follicle destruction (Younglai et al. 2005). Cases of infertility have been reported in several communities due to the use of the pesticide dichlorodiphenyltrichloroethane, which is an endocrine disruptor (Attaran and Maharaj 2000).

4 Conclusion

The aim of this review is to shed light on the risk factors for oocyte aging with the aim of developing new therapeutics that enhance the quality of oocytes and hence the quality of female life. For the sake of maintaining oocyte quality, a healthy lifestyle is crucial. Low caloric intake, caloric restriction, and weight control are very important for inhibiting ROS production in the oocytes of older females and decreasing meiotic spindle shape defects to maintain female fertility. Furthermore, ovarian stimulation regimens have been shown to correct the oocyte microenvironment *in vivo* and improve oocyte quality. Thus, the use of GnRH agonists and antioxidants is beneficial for maintaining oocyte quality. Additionally, avoiding exposure to pesticides and stress maintains female hormonal functions and healthy ovulation. However, we cannot neglect the effects of certain diseases, such as PCOS, $HER2^{+}$ breast cancer, and IR, on oocyte longevity. Moreover, neighbouring cell interactions with oocytes play a pivotal role in maintaining oocyte quality and longevity.

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