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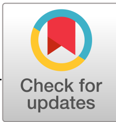

MINI REVIEW

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Action mechanisms of n-3 polyunsaturated fatty acids on the oocyte maturation and developmental competence: Potential advantages and disadvantages

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Infertility is a growing problem worldwide. Currently, in vitro fertilization (IVF) is widely performed to treat infertility. However, a high percentage of IVF cycles fails, due to the poor developmental potential of the retrieved oocyte to generate viable embryos. Fatty acid content of the follicular microenvironment can affect oocyte maturation and the subsequent developmental competence. Saturated and mono-unsaturated fatty acids are mainly used by follicle components as primary energy sources whereas polyunsaturated fatty acids (PUFAs) play a wide range of roles. A large body of evidence supports the beneficial effects of n-3 PUFAs in prevention, treatment, and amelioration of some pathophysiological conditions including heart diseases, cancer, diabetes, and psychological disorders. Nevertheless, current findings regarding the effects of n-3 PUFAs on reproductive outcomes in general and on oocyte quality more specifically are inconsistent. This review attempts to provide a comprehensive overview of potential molecular mechanisms by which n-3 PUFAs affect oocyte maturation and developmental competence, particularly in the setting of IVF and thereby aims to elucidate the reasons behind current discrepancies around this topic.

KEYWORDS
omega-3 fatty acids, oocyte, preimplantation embryo, reproduction

1 | INTRODUCTION

The rate of human infertility, which is defined as a disorder of the reproductive system causing failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (Zegers-Hochschild et al., 2009), is rising according to the recent epidemiological reports (Mascarenhas, Flaxman, Boerma, Vanderpoel, & Stevens, 2012). In vitro fertilization (IVF) is currently the best available therapeutic procedure for infertile couples (Uyar, Torrealday, & Seli, 2013) and a growing cohort of women postponing motherhood (Te Velde, Habbema, Nieschlag, Sobotka, & Burdorf, 2017).

Oocyte quality is one of the crucial factors of female fertility that affects not only fertilization but also subsequent embryo development, implantation, and pregnancy (Rienzi, Vajta, & Ubaldi, 2011). A high percentage of IVF cycles in the United States fails to live birth born due to the poor quality of retrieved oocytes to

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generate viable embryos (Kovalevsky & Patrizio, 2005). Maternal metabolic status and diet directly affect oocyte quality. Indeed, multiple maternal metabolic disorders and deviations including obesity, diabetes, and aging apparently impair oocyte quality through disrupting its mitochondrial function, meiotic spindle array, and chromosomal alignment (D. E. Broughton & Moley, 2017; Schatten, Sun, & Prather, 2014). With respect to diet, oocytes derived from high-fat-fed mice demonstrated significantly higher mitochondrial and meiotic abnormalities compared with the control group (Reynolds, Boudoures, Chi, Wang, & Moley, 2015). Moreover, adherence to the Mediterranean diet appears to be associated with improved pregnancy probability during IVF–intracytoplasmic sperm injection cycles (D. E. Broughton & Moley, 2017). One such an interesting link between maternal metabolism and diet with oocyte quality is fatty acids.

Concentration and relative abundance of lipids and fatty acids in the follicular microenvironment (Fayezi et al., 2014; W. F. A. Marei et al., 2016) or oocyte culture medium (Mardomi et al., 2018) are associated with quality and development during IVF procedure. Three major groups of fatty acids are saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs), corresponding to molecules with no, one, and more than one double bond in their acyl chain, respectively. Additionally, PUFAs are categorized according to the proximity of first double bond to the terminal methyl group (counting as carbon number 1) into omega-3 (n-3), omega-6 (n-6), and omega-9 (n-9) fatty acids. SFAs and MUFAs are primarily utilized by oocyte and surrounding cumulus cells for production of energy and structural elements (reviewed by Dunning, Russell, & Robker, 2014 and Fayezi, Leroy, Ghaffari Novin, & Darabi, 2017). In contrast, PUFAs can play a wide range of roles in oocyte biology and metabolism. Recently, we have described molecular aspects of oocyte maturation and development conducted by n-6 PUFAs, particularly arachidonic acid (AA; Khajeh, Rahbarghazi, Nouri, & Darabi, 2017). Nevertheless, the impact of n-3 PUFAs on oocyte biology and metabolism has received less attention, and thus, it is not fully understood.

Several studies have shown an association of n-3 PUFA consumption with prevention, treatment, and amelioration of some pathophysiological conditions. For example, a recent meta-analysis of 19 observational studies found that the biomarkers of n-3 fatty acids were associated with a lower risk of fatal coronary heart diseases (Del Gobbo et al., 2016). Consumption of n-3 PUFAs reduces the risk of numerous types of cancers, suppresses cancer cell proliferation, and improves the efficacy of anticancer medications (Song & Kim, 2016). Moreover, growing evidence indicates potential benefits of n-3 PUFAs in prevention and treatment of psychopathological disorders such as depression, schizophrenia, cognitive decline, and Alzheimer's disease (Pusceddu, Kelly, Stanton, Cryan, & Dinan, 2016). For these health reasons, many women of reproductive age currently consume supplements of n-3 PUFAs. Nevertheless, eventual effect of n-3 PUFA supplementation on reproductive outcomes, particularly in the setting of IVF treatment, is inconsistent (J. L. Leroy et al., 2014).

This review aims to provide a comprehensive overview of potential mechanisms by which n-3 PUFAs affect oocyte maturation and developmental competence in molecular scale, and thereby to elucidate the reasons behind present inconsistency in the overall effect of dietary n-3 PUFA supplementation on the efficiency of IVF treatment.

2 | ORIGIN OF N-3 PUFAS IN THE FOLLICULAR MICROENVIRONMENT

Due to the lack of delta-12-desaturase and delta-15-desaturase enzymes, animals including human are unable to biosynthesize both linoleic acid (LA; C18:2) and α-linolenic acid (ALA; C18:3) from stearic acid; thus, these are recognized as essential fatty acids and should be supplied by the diet (Calder, 2012). ALA is the simplest and the main dietary n-3 PUFA that can be found in walnut, linseed, rapeseed and relatively lower amounts in soybean and green-leaf plants (Calder, 2012; Welch, Shakya-Shrestha, Lentjes, Wareham, & Khaw, 2010). Availability of ALA in the western diet is around 3.06 g/day, which is 10-fold less than that of LA (Blasbalg, Hibbeln, Ramsden, Majchrzak, & Rawlings, 2011). Although animals cannot produce ALA, they can convert ALA to long-chain n-3 PUFAs including eicosapentaenoic acid (EPA; C20:5) and docosahexaenoic acid (DHA; C22:6) through successive desaturation and elongation reactions (Figure 1; Calder, 2012; Wathes, Abayasekara, & Aitken, 2007; Welch et al., 2010). Nevertheless, this process is restricted to the conversion of only 5% and 0.5% of ALA intake to EPA and DHA, respectively, because of competitive inhibition of delta-6-desaturases by the high amount of dietary LA (Figure 1; Goyens, Spilker, Zock, Katan, & Mensink, 2006; Welch et al., 2010). Furthermore, conversion of ALA to its long-chain derivatives is a tissue-specific process and occurs to a greater extent in women than men (Welch et al., 2010). Therefore, EPA and DHA are not possibly produced sufficiently in the human body and should be received from the diet. Marine-derived foods, particularly from fatty fishes, are rich in long-chain n-3 PUFAs and thus are the major sources of EPA and DHA in human diet (Sioen, Vyncke, De Maeyer, Gerichhausen, & De Henauw, 2013). However, fish intake in most western populations is less than the typical recommended intake (30 g/day), which gives rise to suboptimal receiving of EPA and DHA (Sioen et al., 2013).

Like other types of fatty acids, n-3 PUFAs are present in blood in either free (nonesterified) or esterified forms. Free fatty acids are mainly bound to serum albumin and are transported by circulation to target tissues. Analysis of free fatty acids showed a significant correlation between plasma levels and those of follicular fluid in bovine (J. L. Leroy et al., 2005) and human (Valckx et al., 2012), indicating that plasma-free fatty acids are reflected in the follicular fluid but at lower levels. However, esterified fatty acids in phospholipid, cholesteryl ester, and triglyceride fractions are carried and delivered to tissues by lipoproteins. Main classes of lipoproteins including high-density lipoprotein (HDL), very-low-density lipoprotein (VLDL), intermediate-density lipoprotein, and low-density lipoprotein (LDL) have been detected in the follicular fluid (Von Wald et al., 2010). Nevertheless, HDL is regarded as the sole plasma lipoprotein in the follicular fluid,

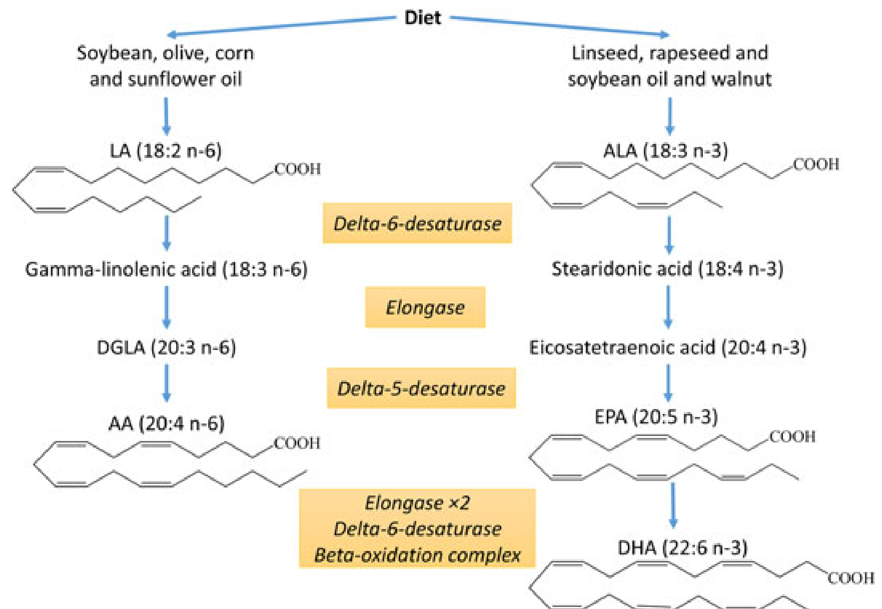

FIGURE 1 Biosynthesis pathway of long-chain PUFAs from LA and ALA. Animals including human can synthesize long-chain n-3 PUFAs from dietary ALA. However, competitive inhibition of enzymes by high concentrations of dietary LA restricts de novo synthesis of long-chain n-3 PUFAs including EPA and DHA. AA: arachidonic acid; ALA: α-linolenic acid; DGLA: dihomo-γ-linolenic acid; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; EPA: eicosapentaenoic acid; LA: linoleic acid; PUFA: polyunsaturated fatty acid [Color figure can be viewed at wileyonlinelibrary.com]

because of follicle basement membrane permeability to up to 100 kDa molecules, excluding VLDL and LDL (Rodgers & Irving-Rodgers, 2010). In support of this, follicular fluid apoA-I and HDL cholesterol were positively correlated with their plasma counterparts (Valckx et al., 2012) whereas there was no similar correlation for VLDL cholesterol (Gautier et al., 2010), indicating that follicular fluid HDL is derived from the circulation, but apoB-containing lipoproteins originate from ovarian cells. Distribution of fatty acids in human follicular fluid is approximately 42% in phospholipids, 34% in cholesteryl ester, and 10% in either triglyceride or free fatty acid fractions, in which palmitic acid (C16:0), stearic acid (C18:0), oleic acid (C18:1; n-9), LA (C18:2; n-6), and AA (C20:4; n-6) are predominant (Shaaker et al., 2012; Valckx et al., 2014). Furthermore, n-3 PUFAs compose 3.7% of total follicular fluid fatty acids, which 93% of them are constituents of phospholipid and cholesteryl ester fractions (Valckx et al., 2014), suggesting the key role of HDL in supplying of ovarian cells with n-3 PUFAs in addition to cholesterol (Table 1). Interestingly, although ALA is the most consumed n-3 PUFA in western populations (Sioen et al., 2013), DHA was the most abundant n-3 PUFA in follicular fluid (Shaaker et al., 2012; Valckx et al., 2014), possibly due to a selective uptake of DHA in the follicular fluid at the expense of ALA. However, these findings need to be interpreted cautiously because more in-depth investigations are required to elucidate fatty acid composition of the follicular fluid in relation to diet composition and the metabolic health of the mother.

According to the analysis of the fatty acid composition of human unfertilized oocytes, 79%, 14%, and 7% of total fatty acids were SFAs, MUFAs, and PUFAs, respectively, with C18:0, C16:0, and C18:1 being the most dominant ones. The ratio of n-3:n-6 PUFAs was also reported to be approximately 1:7 (Matorras et al., 1998). A similar fatty acid profile has also been observed in animal models (Table 1). For example, more than 80% of fatty acids of both bovine cumulus–oocyte complexes (COCs) and sheep oocytes were SFAs (Adamiak, Powell, Rooke, Webb, & Sinclair, 2006; Wonnacott et al., 2010). However, granulosa cells had higher MUFAs, PUFAs, and n-3:n-6 ratios compared with oocyte (Adamiak et al., 2006; Prates et al., 2013; Wonnacott et al., 2010; Table 1), suggesting that effects of n-3 PUFAs on oocyte metabolism may be indirect and mediated by granulosa cells. In this connection, W. F. A. Marei et al. (2017) have recently reported that ALA rescues the oocyte's developmental competence when matured under lipotoxic condition through the restoration of cumulus cell function rather than the oocyte itself.

Because lipid metabolites of plasma are mirrored in the follicular microenvironment, body condition, and diet, which influence the lipid content of circulation, can potentially alter the level and composition of follicle and oocyte lipids. For example, body mass index (BMI) was positively correlated with plasma and follicular fluid triglyceride (Pantasri et al., 2015; Valckx et al., 2012). However, BMI did not appear to correlate tightly with free fatty acids (Jungheim et al., 2011; Valckx et al., 2012) as well as total fatty acid concentration in human

TABLE 1 The content of n-3 PUFAs in follicular compartments

		Total n-3 PUFA content[a]		
References	Species	FF	GCs	Oocyte–COCs
Matorras et al. (1998)	Human	–	–	1.07
Adamiak et al. (2006)	Cattle	–	0.9	0.7
Wonnacott et al. (2010)	Ewe	–	4.1	2.1
Zachut et al. (2010)	Cattle	1.40	0.65	0.00
Shaaker et al. (2012)	Human	1.05	–	–
Moallem et al. (2013)	Cattle	2.78	2.64	2.21
Valckx et al. (2014)	Human	3.7	–	–

Note. COC: cumulus–oocyte complex; FF: follicular fluid; GC: granulosa cell; PUFAs: polyunsaturated fatty acids.
[a]Data are expressed as the mean percentage of total fatty acid (% wt/wt).

follicular fluid (Pantasri et al., 2015; Valckx et al., 2014). Although there is no evidence in human, studies on rodents and ruminants have demonstrated the effects of diet on follicle and oocyte lipid content (Table 2). For example, the inclusion of long-chain n-3 PUFA supplements in the diet of mice (Wakefield et al., 2008) or rats (K. S. Broughton, Bayes, & Culver, 2010) for 4 weeks increased EPA and DHA levels as well as n-3:n-6 fatty acids ratio in ovarian tissue. Similarly, ewes fed with n-3 fatty acid rich diet for a 6-week period exhibited an elevated EPA and reduced AA in both granulosa cells and oocytes (Wonnacott et al., 2010). Moreover, supplementation of cows with linseed oil and fish oil for 60 days increased proportions of ALA and long-chain EPA and DHA in follicular fluid, granulosa cells, and COCs, respectively (Moallem et al., 2013; Zachut et al., 2010). Interestingly, despite the lower levels of EPA and DHA in plasma and follicular fluid, their incorporation into COCs was more than that of ALA, suggesting that incorporation of long-chain n-3 PUFAs into COC may be accomplished more easily than shorter chain counterparts (Moallem et al., 2013). In addition to body condition and diet, there are also pathological abnormalities which modify the fatty acid composition of ovarian tissue. Indeed, Yam et al. (1997) study on the fatty acid composition of ovarian tumors showed a higher n-3 PUFAs in benign tumors compared to cancerous ones. However, no previous study has differentiated fatty acid composition of various types of benign ovarian tumors and normal ovaries. In particular, investigation of fatty acids in fibrothecoma, a benign ovarian tumor, which is associated with lipid-rich theca cells (Takeuchi, Matsuzaki, & Harada, 2012; Yen, Khong, Lamba, Corwin, & Gerscovich, 2013), is interesting.

TABLE 2 Effect of dietary intervention on the fatty acid composition of follicular compartments

Reference	Species	Total n-3 PUFA content[a]	
		Low dietary n-3 PUFAs	High dietary n-3 PUFAs
Follicular fluid			
Zachut et al. (2010)	Cattle	1.40	7.25
Moallem et al. (2013)	Cattle	2.78	6.10
Granulosa cells			
Wonnacott et al. (2010)	Ewe	4.1	20.4
Zachut et al. (2010)	Cattle	0.65	3.44
Moallem et al. (2013)	Cattle	2.64	4.71
Cumulus–oocyte complexes			
Wonnacott et al. (2010)	Ewe	2.1	7.8
Zachut et al. (2010)	Cattle	0.00	4.73
Moallem et al. (2013)	Cattle	2.21	2.44
Ovarian tissue			
Wakefield et al. (2008)	Mouse	6.0	12.1
K. S. Broughton, Bayes, et al. (2010)	Rat	7.5	11.6

Note. PUFA: polyunsaturated fatty acid.
[a]Data are expressed as the mean percentage of total fatty acid (% wt/wt).

3 | IMPACT OF N-3 PUFAs ON OOCYTE MATURATION, FERTILIZATION, AND DEVELOPMENT

Studies addressing the impact of n-3 PUFA supplementation on oocyte maturation and development are listed in Table 3. Studies with in vitro design reported either positive or neutral effect of n-3 PUFA treatment on oocyte maturation and developmental competence. In vitro maturation (IVM) of COCs in the presence of ALA increased oocyte maturation and subsequent embryo development in cow (W. F. Marei, Wathes, & Fouladi-Nashta, 2009) and pig (Lee et al., 2016). Nevertheless, some other studies reported that neither ALA nor EPA treatment affected bovine oocyte maturation and developmental competence during IVM followed by IVF (Leao et al., 2017; W. F. A. Marei et al., 2017; Nikoloff et al., 2017). These contradictory results can originate from treatment with different concentrations and types of n-3 PUFAs as well as an assessment of disparate collection of IVF outcomes (Table 3). Results of in vivo studies in which animal models were supplemented with high dietary n-3 PUFAs before the oocyte pickup and IVF cycles are even more contradictory. In this regard, Moallem et al. (2013) showed that the supplementation of lactating dairy cows with flaxseed oil, as a source of ALA, improved folliculogenesis and in vitro embryo development. On the contrary, flaxseed-supplemented cows exhibited decreased oocyte fertilization and embryo quality according to the Petit, Cavalieri, Santos, Morgan, and Sharpe (2008) study. Similarly, a maternal diet rich in EPA and DHA compromised developmental competence of in vivo fertilized oocytes (Wakefield et al., 2008). Similarly, oocytes derived from patients with fibrothecomas may represent poor fertilization and embryonic development due to probable n-3 PUFA accumulation as discussed above (Yam et al., 1997). Nevertheless, a study by Fouladi-Nashta et al. (2009) corroborated neither positive nor negative effect of flaxseed supplementation on the in vitro reproductive outcomes in lactating dairy cows. Despite the lack of randomized control trials, observational studies on women who underwent IVF treatment also demonstrate a similar contradiction. Accordingly, whereas intake of n-3 PUFAs, particularly ALA and DHA, was found to be associated positively with embryo morphology (Hammiche et al., 2011), Jungheim, Macones, Odem, Patterson, and Moley (2011) reported that serum levels of ALA were dose-dependently associated with decreased embryo implantation and subsequent clinical pregnancy. It seems that these confusing contradictions largely relate to differences in experimental designs of the aforementioned studies. Namely, these studies differ significantly with respect to the type of supplemented n-3 PUFAs (lengths and unsaturation degree of acyl chain), the dietary source of these n-3 PUFAs, a period of dietary intervention, the window of feeding, and the type of studied species, which ultimately cause incompatible reproductive outcomes (Table 3). In support of this, Ponter, Guyader-Joly, Nuttinck, Grimard, and Humblot (2012) found that effect of fat supplementation on oocyte fertilization and cleavage changed over the intervention time in a group of dairy heifers, regardless of supplement nature. In addition to

TABLE 3 Studies evaluated the impact of n-3 PUFA supplementation on oocyte maturation and developmental competence

Reference	Species (n)	Intervention method	n-3 PUFA dose; period of intervention; comparison
Positively effective			
W. F. Marei et al. (2009)	Cattle	In vitro	50 μM ALA; 24 hr; FFA-free BSA
Zachut et al. (2010)	Cattle (24)	In vivo	3.8% linseed oil (242.2 g/day ALA); 94 days; 1% Megalac[a]
Moallem et al. (2013)	Cattle (42)	In vivo	Group 1: 2.9% linseed oil (131.0 g/day ALA), group 2: 2.9% fish oil (13.5 g/day EPA and 10.0 g/day DHA); 100 days; 560 g/day SFAs (100%)
Lee et al. (2016)	Pig	In vitro	100 μM ALA; 33 hr; FFA-free BSA
Negatively effective			
Petit et al. (2008)	Cattle (30)	In vivo	7.9% linseed (56.8% ALA); 80 days; 2.8% megalac (89.1% SFAs and MUFAs)
Wakefield et al. (2008)	Mouse	In vivo	7% fat (19.09% total n-3 PUFAs); 28 days; 7% fat (91.57% SFAs and MUFAs)
Nikoloff et al. (2017)	Cattle	In vitro	1 mM EPA; 24 hr; solvent control
Ineffective			
Fouladi-Nashta et al. (2009)	Cattle (12)	In vivo	11.4% linseed oil (48% ALA); 25 days; 2.8% megalac (74% SFAs and MUFAs)
Wonnacott et al. (2010)	Ewe (36)	In vivo	1% linseed oil + 3.5% fish oil; 42 days; 4.5% sunflower oil
Ponter et al. (2012)	Cattle (18)	In vivo	12.1% flaxseed oil (26.7% ALA); 42 days; 12.1% soybean oil (25.5% LA)
W. F. A. Marei et al. (2016)	Cattle (6)	In vivo	11.5% linseed + 1.5% linseed oil; 28 days; hay-based control
Leao et al. (2017)	Cattle	In vitro	100 μM ALA; 22 hr; 10% FCS
W. F. A. Marei et al. (2017)	Cattle	In vitro	50 μM; 22–24 hr; FFA-free control

Note. Values provided inside and outside the parentheses are percentages of the specified food ingredient in daily dry food mass intake and percentages of the specified omega-3 fatty acid in the food ingredient, respectively. ALA: α-linolenic acid; BSA: bovine serum albumin; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; FCS: fetal calf serum; FFA: free fatty acid; LA: linoleic acid; MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid; SFA: saturated fatty acid (Volac Wilmar Feed Ingredients, United Kingdom).

[a]Calcium salts of palm fatty acids.

lack of consensus, lack of mechanistic insights regarding the impact of n-3 PUFAs on reproduction is also another limitation of the above-mentioned studies. Hence, more studies are essential to differentiate the impact of n-3 PUFAs from those of other types of fatty acids including MUFAs and/or n-6 PUFAs, which are also present in dietary sources of n-3 PUFAs in considerable proportions.

4 | MECHANISMS BY WHICH N-3 PUFAs INFLUENCE OOCYTE MATURATION, FERTILIZATION, AND DEVELOPMENT

Numerous biological and cellular processes contribute to oocyte maturation, fertilization, and development, with some of these being identified as action targets for n-3 PUFAs. The following sections address potential mechanisms by which n-3 PUFAs influence the mentioned reproductive processes.

4.1 | N-3 PUFAs act as endogenous activators of peroxisome proliferator-activated receptors (PPARs)

PPARs as nuclear receptors are involved in the regulation of various cellular processes including energy homeostasis, inflammation, and tissue remodeling (Nakamura, Yudell, & Loor, 2014). In contrast to other nuclear receptors, a ligand-binding pocket of PPARs is relatively large, allowing a vast range of natural and synthetic ligands to bind and activate them (Nakamura et al., 2014). Upon ligand binding, PPAR forms a heterodimer with retinoid X receptor (RXR) and then binds to PPAR response element, which is located in promoter and thereby regulates transcription of target genes (Nakamura et al., 2014). Expression of all three PPAR isoforms, including PPARα, PPARβ/δ, and PPARγ, has been identified in ovarian tissue. PPARβ/δ is expressed ubiquitously in ovarian cells whereas PPARα and PPARγ were primarily found in the theca and granulosa cells, respectively (Komar, 2005). Nevertheless, immunofluorescence experiments recently have identified expression of all three PPAR isoforms and their RXR counterparts (α, β, and γ) in the human preovulatory granulosa cells (Tatone et al., 2016). In the rat ovary, expression of PPARα and β/δ remains stable in different stages of follicular development whereas PPARγ expression increases with follicle growth but then is dramatically downregulated in response to LH surge (Komar, 2005). In addition to common signaling pathway, PPARγ ligands can bind and activate cell surface G protein–coupled receptor 40, a process that initiates phosphorylation cascade leading to PPARγ activation (Wang et al., 2015).

Both n-6 and n-3 PUFAs, and their eicosanoid derivatives are the main endogenous activators of PPARs (Sampath & Ntambi, 2005). These fatty acids bind to PPARs in the micromolar scale. Disassociation constants, K_d, of PPAR–PUFA complexes have been determined in a range of 1–5 μM (Marion-Letellier, Savoye, & Ghosh, 2016). Considering the low concentration of free PUFAs in the follicular fluid (0.2–1.5 μM; Valckx et al., 2014), PUFAs would not saturate ovarian cell PPARs. Thus, these fatty acids can act as key endogenous regulators of PPARs. Notably, due to the large size of PPAR ligand-binding site, the affinity of long-chain fatty acids for PPARs is more than that of

short- and medium-chain fatty acids (Marion-Letellier et al., 2016; Nakamura et al., 2014). Therefore, DHA is expected to bind and activate PPARs stronger than AA and EPA. In addition to the abundance of natural activators, several synthetic ligands with therapeutic and commercial objectives have been developed for PPAR isoforms (Sampath & Ntambi, 2005). Of these exogenous agonists, fibrates (e.g., bezafibrate and clofibrate) and thiazolidinedione (e.g., rosiglitazone and pioglitazone) preferentially bind to and activate PPARα and γ, respectively (Sampath & Ntambi, 2005). Because of the specificity of these synthetic agonists for PPAR isoforms, most investigations on the role of PPARs in the reproduction have used these compounds instead of natural ligands.

PPARs are key regulators of steroidal sex hormones including estradiol and progesterone. These steroid hormones, in turn, play pivotal roles in follicle growth and differentiation (Ting, Xu, & Stouffer, 2015), oocyte maturation (Liu et al., 2017), and embryo development (Aparicio et al., 2011). Activation of PPARα leads to reduced aromatase (CYP19A1; an androgen-to-estrogen converting enzyme) expression and activity (Lovekamp-Swan, Jetten, & Davis, 2003; Toda, Okada, Miyaura, & Saibara, 2003), upregulation of 17β-hydroxysteroid dehydrogenase (17βHSD) IV (estradiol-to-estrone converting enzyme), and reduced estradiol biosynthesis and availability in granulosa cells (Komar, 2005; Tatone et al., 2016). Similarly, ligand-bound (activated) PPARγ suppresses the expression of aromatase in mouse and human granulosa cells in vitro (Bloom, Mok-Lin, & Fujimoto, 2016; Shahnazi et al., 2015) probably through disrupting the interaction of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) with aromatase promoter II (Fan et al., 2005). Furthermore, PPARγ attenuates estradiol production by reducing biosynthesis of its androgenic precursor testosterone in theca cells (Seto-Young et al., 2005). Nevertheless, some studies reported that neither aromatase expression nor estradiol output was affected by upregulation of PPARγ in human granulosa cells in vitro (Chen et al., 2009; Tatone et al., 2016). With respect to the effect of PPAR activation on progesterone biosynthesis, current data are inconsistent. Despite the inverse association of PPARγ expression pattern with both cholesterol side-chain cleavage enzyme (P450SCC or CYP11A1; Komar & Curry, 2003) and 3βHSD II (Tatone et al., 2016), endogenous (PGJ_2) and exogenous (TZDs) ligands of PPARγ promoted progesterone secretion in ovarian granulosa cells (Komar & Curry, 2003; Komar, Braissant, Wahli, & Curry, 2001; Seto-Young et al., 2005). However, Chen et al. (2009) observed no alteration in P450SCC and 3βHSD II expressions and secreted progesterone level in granulosa cell culture upon treatment with either PPARγ agonist or antagonist. This inconsistency on the effect of PPAR activation on progesterone biosynthesis may be attributed to the difference in cell type, ovarian hyperstimulation regime, and/or species type. It has been noted that, regarding the nonspecific interaction of PUFAs with all three PPAR isoforms, the effect of n-3 PUFAs on steroidogenesis may depend on the fine balance among expressions of PPAR isoforms in oocyte microenvironment.

In addition to steroid hormone metabolism, PPARs influence metabolic properties of COC (Morin-Dore et al., 2017). Fatty acid β-oxidation of cumulus cells is a pivotal process for supplementation of the oocyte with adenosine triphosphate (ATP). Whereas PPARα activation showed no effect during IVM of mouse COCs, rosiglitazone, a specific ligand of PPARγ, dose-dependently reduced both β-oxidation and embryo blastocyst formation (Dunning, Anastasi, Zhang, Russell, & Robker, 2014). Nevertheless, transcription of genes involved in the β-oxidation, including acyl-CoA synthetase (*Acsl1*), carnitine palmitoyltransferase (*Cpt1b* and *Cpt2*), and acetyl-CoA transferase (*Acaa2*), was enhanced in the rosiglitazone-treated COCs (Dunning, Anastasi, et al., 2014). Inhibited β-oxidation, even in enhanced gene expression, may occur due to a crosstalk activation of insulin signaling pathway (Seto-Young et al., 2007), in which PPARγ agonists upregulate insulin receptor and insulin receptor substrate-1 expression in ovarian cells. Activation of insulin signaling is associated with an increase in cellular malonyl-CoA levels, which in turn lower fatty acid β-oxidation through allosteric inhibition of CPT1 (Schreurs, Kuipers, & van der Leij, 2010). In addition, upregulation of β-oxidation by PPARs is speculated to carry out through induction of malonyl-CoA decarboxylase, a degradative enzyme of malonyl-CoA, not CPT1 (Nakamura et al., 2014). PPARα ligands increase fatty acid β-oxidation in some cell lines and tissues (Kersten & Stienstra, 2017). In return, PPARγ ligands are known to increase fat storage with a concomitant decrease in β-oxidation (Janani & Ranjitha Kumari, 2015; Roberts et al., 2011). With regard to the relatively more active role of PPARγ compared to PPARα in regulating COC functions, n-3 PUFAs may induce fatty acid storage as neutral lipid droplets rather than β-oxidation in the COC (Dunning, Anastasi, et al., 2014). Promoted cumulus expansion in the presence of specific PPARγ ligands (i.e., rosiglitazone) due to increased matrix production is also in line with this idea (Dunning, Anastasi, et al., 2014). Taken together, the ability of n-3 PUFAs in the activation of PPARs allows these fatty acids to regulate homeostasis of steroid hormones and fatty acids and thereby influence oocyte maturation, fertilization, and development. It can be concluded that the activation of PPARs, particularly PPARγ, by n-3 PUFAs compromises oocyte maturation and developmental competence through impairing follicular steroidogenesis and fatty acid β-oxidation.

4.2 | N-3 PUFAs alter follicular prostaglandin (PG) biosynthesis

PGs are a group of PUFA-derived compounds which act as signaling agents mediating various processes including inflammation (Rossitto, Ujjan, Poulat, & Boizet-Bonhoure, 2014). Twenty carbon PUFAs including n-6 dihomo-γ-linolenic acid (DGLA, C20:3), n-6 AA, and n-3 EPA act as precursors for biosynthesis of 1-, 2-, and 3-series of PGs, respectively (Figure 2). However, 1- and 3-series PGs are physiologically less active than AA-derived PGs (Wada et al., 2007). As reviewed by Rossitto et al. (2014), biosynthesis of PGs starts with the release of DGLA, AA, or EPA from plasma membrane via phospholipase A2, followed by the rate-limiting action of cyclooxygenase (COX), producing corresponding PGH, which is converted to final PGs by respecting synthases. Ultimately, PGs are transported to extracellular space, wherein they exert their effects via

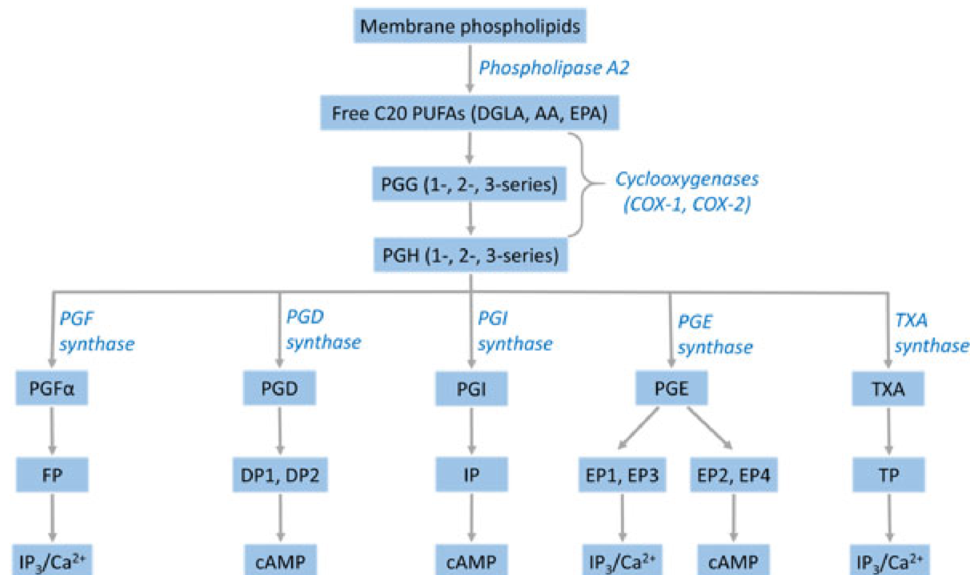

FIGURE 2 Schematic pathway of PG biosynthesis and mode of action. Phospholipase A2 releases 20 carbon DGLA, AA, and EPA from membrane phospholipids in which the action of COXs is converted firstly to 1-, 2- and 3-series PG endoperoxide (PGG) and then to corresponding PGH, respectively. Subsequently, PGHs are converted to final PGs (PGFα, PGD, PGI, and PGE) and TXA by the action of respective synthases. After biosynthesis, each PG is released to extracellular space which binds to a subfamily of G protein–coupled receptors (FP, DP1, DP2, IP, EP1-4, and TP) and initiates various downstream signaling pathways including cyclic adenosine monophosphate and/or IP_3–Ca^{2+}. AA: arachidonic acid; COX: cyclooxygenase; DGLA: dihomo-γ-linolenic acid; DP: prostaglandin D receptor; EP: prostaglandin E receptor; EPA: eicosapentaenoic acid; FP: prostaglandin F receptor; IP: prostacyclin receptor; IP_3: inositol 1,4,5-trisphosphate; PGH: prostaglandin H; TP: thromboxane A receptor; TXA: thromboxane A [Color figure can be viewed at wileyonlinelibrary.com]

binding to a specific family of G protein–coupled receptors (Figure 2).

As outlined above, COX is a central enzyme in PG biosynthesis. Two isoforms of COX have been characterized, differing in encoding genes, cellular and subcellular distribution, and expression pattern, that is, COX-1 and COX-2. However, there is a general consensus that most follicular PGs are produced by COX-2 (Duffy, 2015). Upon gonadotropin stimulation, COX-2 is induced in cumulus-granulosa cells, followed by a release of large amounts of PGE_2 into the follicular fluid. PGE_2 is the major PG of oocyte microenvironment (reviewed by Sugimoto, Inazumi, & Tsuchiya, 2015), which mediates cumulus expansion, oocyte meiotic resumption (Blaha, Prochazka, Adamkova, Nevoral, & Nemcova, 2017), and supports embryo development (Nuttinck et al., 2017). Despite the positive effects of PGE_2, its excessive levels are associated with impaired oocyte meiosis and fertilization (Duffy, McGinnis, VandeVoort, & Christenson, 2010). Therefore, it can be said that balanced biosynthesis of PGE2 is essential for achieving appropriate oocyte maturation and development.

n-3 PUFAs moderate production of 2-series PGs through a decline in the incorporation of AA in the second carbon of glycerol backbones (sn-2) sites of membrane phospholipids and competitive inhibition of COX enzymes (Figure 3; Wada et al., 2007). In vitro treatment of bovine COCs with a physiological concentration of ALA (50 μM) resulted in PGE_2 increment in the culture medium, which was associated with the promotion of oocyte maturation, cleavage, and blastocyst rate (W. F. Marei et al., 2009). However, supplementation of mice with human-achievable doses of n-3 PUFAs (ALA or combination of EPA and DHA) improved ova release, which was not necessarily associated with PGE increment (K. S. Broughton, Bayes, et al., 2010; Trujillo & Broughton, 1995). Notably, ova release was associated with reduced AA and increased EPA levels of ovarian phospholipids. Thus, it can be suggested that the enhancement of ovulation by n-3 PUFAs might be due to a shift in the biosynthesis of PGE_2 toward less active PGE_3, which prevents antiovulatory effects of excessive PGE_2 (K. S. Broughton, Bayes, et al., 2010). Furthermore, the expression of enzymes involved in PG biosynthesis was altered following in vitro and in vivo n-3 PUFA supplementation. Human granulosa cell culture in the presence of EPA displayed significantly reduced COX-2 expression (Shahnazi et al., 2015) possibly because of the PPAR activation. Indeed, long-chain n-3 PUFAs activate PPARs, which in turn interact physically with NF-κB, arresting its traverse to the promoter of target genes including COX-2 (Calder, 2012). Nevertheless, a higher ratio of n-3:n-6 fatty acid dairy diet not only did not affect gene expression of COX-2 but also increased PGE synthase 1 (PTGES1), suggesting a compensatory mechanism for AA reduction to synthesize sufficient PGE_2 levels required for oocyte maturation and development (Ponter et al., 2012). In consistent with this finding, EPA supplements increased PGE_2 levels without affecting gene expression of COX-2 in mice ovaries (K. S. Broughton, Rule, et al., 2009). Overall, n-3 PUFAs can improve oocyte maturation and developmental competence through moderating COX-2-mediated inflammatory processes while providing sufficient levels of PGE_3 through upregulation of PTGES1. Contradictions in the impact of n-3 PUFA on either

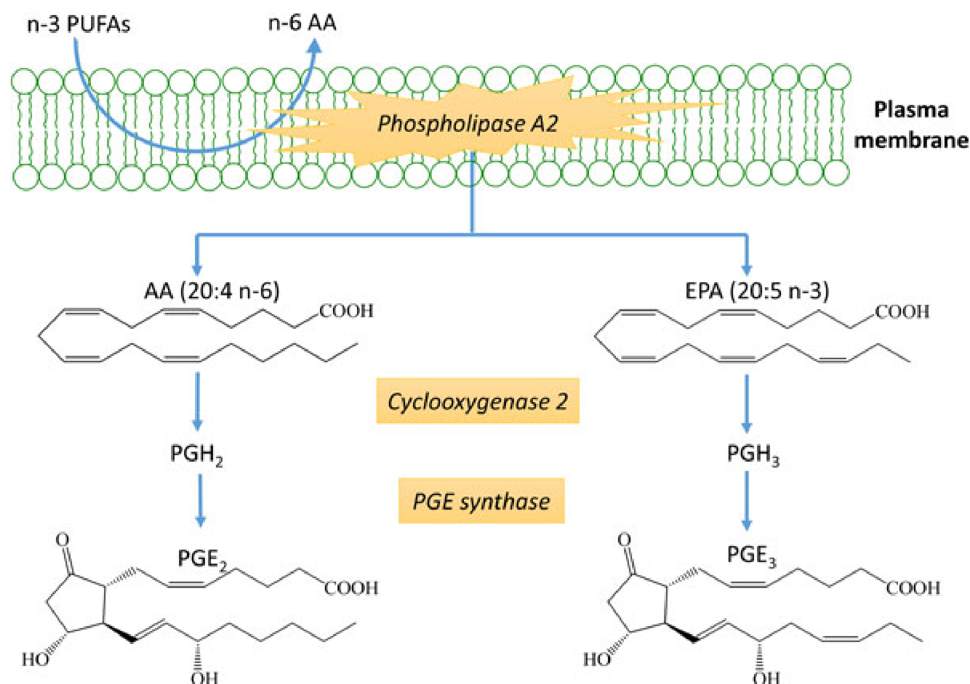

FIGURE 3 Mechanisms by which dietary n-3 PUFAs moderate production of PGE_2. n-3 PUFAs, particularly EPA, are replaced with AA residues of plasma membrane phospholipids. In addition, EPA competes with AA for the active site of cyclooxygenase enzyme, leading to decreased PGE_2 and increased PGE_3 production. PGE_3 is physiologically less active than PGE_2, possibly due to the structural difference among them. AA: arachidonic acid; EPA: eicosapentaenoic acid; PGE: prostaglandin E; PUFA: polyunsaturated fatty acid [Color figure can be viewed at wileyonlinelibrary.com]

PGE_2 production or reproductive parameters might be the consequence of differences in type and dose of fatty acids, lack of specificity in PGE_2 and PGE_3 detection, and comparison of in vitro outcomes with those of in vivo.

4.3 | N-3 PUFAs disrupt the order of membrane lipid rafts

According to the modern definition, the plasma membrane is a dynamic mosaic bilayer in which proteins and lipids are distributed in the lowest achievable free energy status (Head, Patel, & Insel, 2014). However, distribution of plasma membrane components is not homogenous throughout the lipid bilayer. Nanoscale membrane domains enriched in sphingolipids, cholesterol, and SFA-rich phospholipids are known as lipid rafts. Most of the membrane proteins accumulate in these lipid domains, which act as platforms for the assembly of membrane proteins, including proteins involved in signal transduction (Head et al., 2014). The role of lipid rafts in oocyte plasma membrane function, maturation, and development has been investigated in various mammalian species including mouse (Comiskey & Warner, 2007), pig (Sasseville et al., 2009), and human (Van Blerkom & Caltrider, 2013). During IVM of porcine COCs, lipid rafts act gonadotropin-dependently as inactivation sites for connexin-43. Connexin-43 is a structural unit of gap junctions that causes breakdown of gap junction communication between somatic cells and oocyte, which is essential for meiotic resumption (Sasseville et al., 2009). Study of unfertilized human oocytes showed that not only attachment of sperm to oocyte initially took place in lipid rafts but also the configuration of lipid rafts affected sperm adhesion and penetration ability, indicating the key role of lipid rafts in oocyte fertilization (Van Blerkom & Caltrider, 2013). Consistently, disrupting lipid rafts by depletion of cholesterol from the plasma membrane of mouse oocytes led to decreased fertilization rate and delayed second polar body extrusion (Buschiazzo et al., 2013). The enrichment of lipid rafts in cleavage furrow of developing embryo together with the failed embryo development to the blastocyst stage due to the cholesterol depletion indicated the necessity of lipid rafts for preimplantation development of the embryo in addition to oocyte maturation and fertilization (Comiskey & Warner, 2007).

Lipid rafts of the plasma membrane are inversely associated with n-3 PUFA content (Shaikh, 2012). Conformational flexibility of acyl chains of n-3 PUFAs results in their low affinity to cholesterol and sphingomyelin. Thus, incorporation of n-3 PUFAs in plasma membrane disrupts order and spatial distribution of lipid raft domains through dispersing raft-forming compounds in the plasma membrane (Turk & Chapkin, 2013). To the best of our knowledge, there is no study linking n-3 PUFAs supplementation and organization of lipid rafts in the oocyte. However, lipidomic analysis of *Xenopus* oocyte has demonstrated that fertilization is accompanied by an increment in SFAs, particularly long-chain types, in the sphingomyelin fraction (Petcoff, Holland, & Stith, 2008). Substitution of SFAs with n-3 PUFAs in oocytes lipids can potentially compromise fertilization by perturbing lipid rafts. Disruption of lipid rafts by n-3 PUFAs alters the distribution and function of raft-localized proteins, which in turn

affect cell signaling, gene expression, and ultimately cell function. For instance, $CD4^{+}$ T cells from fish oil–fed mice showed reduced recruitment of signaling proteins such as protein kinase C (PKC) and phospholipase C (PLC) in the membrane and attenuated cell activation and proliferation (Turk & Chapkin, 2013). Interestingly, sperm-induced activation of PLC, which ultimately results in activation of PKC, is considered as the main event during oocyte fertilization (Kawano, Yoshida, Miyado, & Yoshida, 2011; Petcoff et al., 2008). Taken together, large incorporation of n-3 PUFAs in the oocyte membrane in consequence of n-3 PUFA supplementation can destabilize lipid rafts, reduce clusters of signaling proteins in the membrane, and thereby adversely affect oocyte maturation, fertilization, and development.

4.4 | N-3 PUFAs are susceptible to lipid peroxidation

Reactive oxygen species (ROS) in physiological concentrations function as messengers in critical signaling transduction in reproductive pathways, and low levels of ROS have been linked to cellular dysfunction (Henkel, 2011). However, excess production of ROS can induce oxidative stress and negatively affects cellular homeostasis in gametes and germ cells (Sinha & Gupta, 2018). Regardless of ROS type, ROS-mediated cellular damage initiates with oxidative degradation of membrane lipid components such as phospholipids, the process that is called lipid peroxidation (Kwiecien et al., 2014; Mihalas, De Iuliis, Redgrove, McLaughlin, & Nixon, 2017). This process leads to the generation of a wide range of detachment products including peroxyl radicals, hydroperoxides, and ultimately secondary detachment products. The extent of lipid peroxidation can be evaluated by the quantification of secondary detachment products, mainly malondialdehyde, 8-isoprostaglandin F2α (F2-IsoP), and reactive aldehyde species (Kelley, Yoshida, & Erickson, 2014). Some studies have reported an inverse relationship between lipid peroxidation biomarkers and IVF success. For example, levels of follicular fluid MDA were negatively correlated with meiotic maturation of oocytes, fertilization rate, and good quality embryo (Chattopadhayay et al., 2010; Rashidi et al., 2014; Singh, Chattopadhyay, Chakravarty, & Chaudhury, 2013). Additionally, Jana et al. (2010) not only reported a negative association between follicular fluid MDA and IVF outcomes but also estimated an upper limit value for ROS in follicular fluid beyond which corresponding oocytes had compromised fertilization and embryo quality. Nevertheless, some evidence indicated positive correlations of oxidative stress index of follicular fluid with serum E2 level, retrieved mature oocyte, and embryo cleavage, which can be attributed to high metabolic rate in healthy follicles (Velthut et al., 2013; Wiener-Megnazi et al., 2004). Altogether, although the moderate concentration of ROS and lipid peroxides reflects the active metabolism of a healthy follicle, high levels of them are unfavorable for oocyte and embryo quality.

Owing to the high grade of unsaturation, n-3 PUFAs greatly tend to be peroxidated and fragmented by ROS and produce secondary detachment products (Kelley et al., 2014). Nevertheless, it is debatable whether or how n-3 PUFA supplements influence lipid peroxidation in human because of the diversity of lipid peroxidation biomarkers in the literature (Kelley et al., 2014). Most studies based on MDA assay have reported an increase in lipid peroxidation following administration of n-3 PUFA supplements. In comparison, studies that measured F2-IsoP as a biomarker have reported a decline in lipid peroxidation (Kelley et al., 2014). However, F2-IsoP is a specific biomarker for AA peroxidation and thus does not appear to be a proper biomarker for evaluating lipid peroxidation of n-3 fatty acids. In return, MDA is generated by peroxidation of fatty acids with at least three double bonds and can be served as a peroxidation biomarker of both n-3 and n-6 PUFAs (Kelley et al., 2014). Therefore, supplementation of n-3 PUFAs appears to correlate with increased lipid peroxidation. Lipid peroxides of n-3 PUFAs alter the physicochemical properties of cellular membranes, leading to perturbations in membrane integrity, permeability, and electric potential (Kelley et al., 2014; Kwiecien et al., 2014). Furthermore, these compounds have more stability than oxygen radicals allowing them to traverse cell membranes and propagate free radicals beyond their production spot (Kelley et al., 2014). Accordingly, these lipid peroxides of n-3 PUFAs can potentially lead to peroxidation of non-n-3 PUFAs as a secondary detrimental effect. On the other hand, their secondary detachment products due to their electrophilic trait are capable to form covalent adducts with the cysteine, histidine, and lysine residues of cellular proteins, giving rise to protein crosslinking, structural denaturation, and protein dysfunction (Kwiecien et al., 2014; Mihalas et al., 2017). In this regard, condensation of 4-hydroxy-7-oxo-5-heptenoic acid (HOHA), specific product of DHA peroxidation, with lysyl residues of proteins was found to generate 2-ω-carboxyethylpyrrole protein adducts, which in turn intensifies tumor growth, atherosclerosis, and inflammation through recruitment of toll-like receptors (TLRs), particularly TLR2 (Yakubenko & Byzova, 2017). In addition to HOHA, 4-hydroxyhexenal (4-HHE), a reactive aldehyde generated by n-3 PUFA peroxidation, also contributes to adduction with cellular proteins (Long & Picklo, 2010). Recently, Mihalas et al. (2017) have depicted that treatment of mice oocytes with 4-hydroxynonenal (4-HNE), an n-6 PUFA-derived analog of 4-HHE, compromises oocyte meiotic resumption, spindle assembly, and chromosomal alignment. They have also demonstrated that these deleterious effects were mediated through adduction of 4-HNE with tubulin proteins, leading to microtubule segregation (Mihalas et al., 2017). Owing to similar electrophilic nature, 4-HHE is potentially able to form same adducts and thus exert similar adverse effects (Long & Picklo, 2010). On the other hand, reactive aldehyde species such as 4-HHE serve as activators of the NF-κB pathway, which in turn plays the major role in stimulation of cytokine production and inflammatory response (Long & Picklo, 2010; Łuczaj, Gęgotek, & Skrzydlewska, 2017; Yadav & Ramana, 2013). There is evidence indicating a tight downregulation of NF-κB activity in bovine oocytes during the transition from germinal vesicle to fully matured oocyte (Paciolla et al., 2011). Supportively, elevated levels of inflammatory cytokines in the follicular fluid were found to correlate with impaired oocyte maturation (Opoien et al., 2013).

Therefore, despite the lack of direct evidence, it can be concluded that 4-HHE potentially impairs oocyte maturation through induction of NF-κB activity and inflammatory response in the oocyte micro-environment. Notably, the toxic effects of 4-HHE may be of greater importance as there is a significant elevation in free 4-HHE levels by daily DHA supplementation (Soulage et al., 2018). Interestingly, mice fed on a diet with relatively high n-3 PUFAs displayed DHA enrichment in the ovarian tissue with concomitant increased oxidative stress and compromised embryo cleavage and blastocyst generation (Wakefield et al., 2008). Similarly, ALA dramatically arrested the development of both pronuclear and two-cell embryos in mice, which was reversed by addition of antioxidants. LA and AA also induced the same effects, but at relatively lower degrees compared with ALA (Nonogaki, Noda, Goto, Kishi, & Mori, 1994). In addition to animal models, human studies have reported a relationship between n-3 PUFAs and peroxidation biomarkers in the follicular environment as well. For example, Fujimoto et al. (2011) estimated a positive correlation between follicular levels of 13-hydroxyoctadecatrienoic acid (13-HOTE, product of ALA oxidation) and embryo fragmentation score. In another report, dietary intake of PUFA by women undergoing IVF was positively correlated with follicular fluid MDA, which itself had an inverse relationship with embryo cleavage rate and numbers of blastomeres (Kazemi, Ramezanzadeh, Nasr-Esfahani, Saboor Yaraghi, & Ahmadi, 2013). Nevertheless, there is no distinction between n-6 and n-3 PUFAs in this study, restricting the interpretation of its findings to some degrees. Taken together, the susceptibility of n-3 PUFAs to peroxidation is increased due to a relatively high oxidative stress in a metabolically active environment of the follicle. Products of n-3 PUFA peroxidation, in turn, can adversely affect oocyte meiotic resumption, fertilization, and particularly embryo development through modification of cell membrane properties, the formation of deleterious protein adducts, and induction of inflammation. However, future elucidation of the exact effect of n-3 PUFAs on lipid peroxidation level as well as embryogenesis requires an evaluation of specific peroxidation biomarkers. Such an evaluation would be of great importance regarding blunt and blind advice to dramatically change diets toward n-3 PUFA-rich diets, as there is the risk of increased susceptibility to lipid peroxidation.

5 | SUMMARY AND CONCLUSIONS

It is known that n-3 PUFAs have more than one double bond, with the first one located on the carbon 3 from the terminal methyl group. ALA, the simplest member of n-3 PUFAs, acts as a precursor for more biologically active long-chain n-3 PUFAs through consecutive desaturation and elongation reactions. Because production of long-chain n-3 PUFAs from ALA by this process is limited, dietary intake is required to supply optimal amounts of these essential fatty acids. Although n-3 PUFAs represent a small portion of fatty acids in follicles, the relative abundance of n-3 PUFAs in granulosa cells is physiologically more than that of oocyte. Thus, it can be suggested that n-3 fatty acids regulate oocyte maturation and development predominantly by altering metabolism and function of granulosa cells through regulating PPARs. Activation of PPARγ reduces production of estradiol, progesterone, and β-oxidation-derived ATP in cumulus-granulosa cells, which have a negative influence on viability and development of the embryo. In contrast, n-3 PUFAs appear to replace 2-series PGs with 3-series analogs by moderating gene expression and activity of COX-2 leading to promoted ovulation, oocyte maturation, and embryo development. Some of the effects of n-3 PUFAs are in relation to change in the fatty acid composition of plasma lipid bilayer. Incorporation of n-3 PUFAs, in particular long-chain types, in plasma membrane disrupts lipid raft order and elevates lipid peroxidation in the COCs.

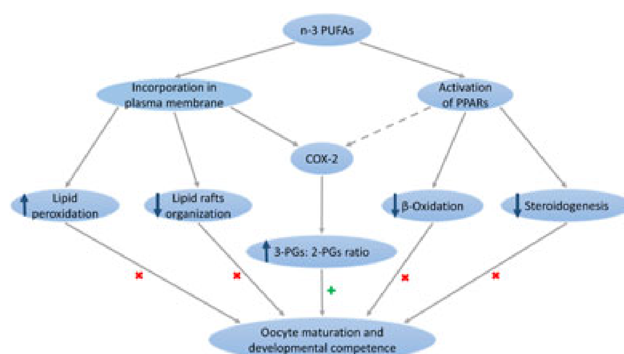

FIGURE 4 Schematic model indicating mechanisms by which n-3 PUFAs influence oocyte maturation and developmental competence. Accordingly, n-3 PUFAs have both beneficial and detrimental effects on fertility, but their inhibitory effect on oocyte maturation, fertilization, and embryo development might prevail in n-3 PUFA dietary supplementation. COX: cyclooxygenase; PGs: prostaglandins; PPAR: peroxisome proliferator-activated receptor; PUFA: polyunsaturated fatty acid [Color figure can be viewed at wileyonlinelibrary.com]

In conclusion, n-3 PUFAs are able to exert both advantageous and disadvantageous effects on oocyte maturation and developmental competence through modulation of metabolic pathways and membrane properties of COC (Figure 4). However, according to our literature review the negative effects of n-3 PUFA supplementation on oocyte maturation and development prevail over the positive effects. Nevertheless, variations in consumption dosage, period, window of n-3 PUFA supplementation, and metabolic status of the mother can most probably alter the interaction between discussed mechanisms and, in consequence, lead to relative reproductive outcomes. Thus, prescription of n-3 PUFAs with the aim to improve oocyte maturation and developmental competence in the setting of IVF treatment requires more detailed insights about action mechanisms of n-3 PUFAs and the interactions among them.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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