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The Role of Dietary and Lifestyle Factors in the Formation of Premature Ovarian Insufficiency

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Abstract*— Premature ovarian insufficiency (POI) is a complex medical condition characterized by the early depletion of ovarian follicles, leading to diminished ovarian function before the age of 40. This condition can manifest in various ways, including early menopause, which is defined as the cessation of menstrual periods for a full year, and a significant reduction in fertility potential. The consequences of POI can be profound and deeply affect a woman's physical and emotional health, as it often leads to symptoms commonly associated with menopause, such as hot flashes, night sweats, and mood changes. Additionally, women with POI may face challenges related to infertility, which can have a significant psychological impact. Recent research has begun to shed light on the multifaceted nature of POI, revealing that oxidative stress plays a crucial role in its development and progression. Oxidative stress refers to an imbalance between free radicals, which are unstable molecules that can cause cell damage, and antioxidants, which help neutralize these harmful substances. Excessive oxidative stress can lead to the premature aging of ovaries and a reduction in the quality and quantity of ovarian follicles. Moreover, emerging evidence suggests that lifestyle factors, particularly dietary habits, can significantly influence the risk of developing POI. A diet rich in antioxidants, vitamins, and minerals may help mitigate oxidative stress, potentially protecting ovarian function. For instance, foods high in omega-3 fatty acids, such as fatty fish, as well as fruits and vegetables packed with antioxidants, can contribute to overall reproductive health. Integrating a balanced diet that prioritizes these nutrient-rich foods may not only support ovarian health but also delay the onset of menopause. In addition to dietary considerations, other lifestyle interventions, including regular physical activity and stress management techniques, can also play a role in reducing the risk of POI. Regular exercise has been shown to improve overall health and may help regulate hormonal balances that are vital for

reproductive function. Stress management through mindfulness, yoga, or other relaxation techniques can further support hormonal health and enhance overall well-being. This review underscores the critical interplay between oxidative stress and lifestyle factors in the context of premature ovarian insufficiency. By recognizing the impact of diet and lifestyle choices, targeted interventions can be developed to help reduce or even delay the onset of POI. This proactive approach could empower women to take charge of their reproductive health, promoting better outcomes and enhancing their quality of life as they navigate the challenges associated with early ovarian insufficiency. Ultimately, a deeper understanding of these factors provides a pathway for more effective prevention and management strategies for those at risk.

Keywords—premature ovarian insufficiency, oxidative stress, exercise, dietary factors, lifestyle factors, nutrition, reproductive health, infertility, risk factors and women's health

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I. INTRODUCTION

Premature Ovarian Insufficiency (POI), also called early menopause by many, is when a woman is out of follicles from her ovaries or when the follicles are no longer responding to normal hormonal stimulation in women below the age of 40 years [1], thereby leading to early menopause. Menopause usually is the apex of a woman's reproductive journey, and the average age this should occur is between 50-52 years. The good thing is, unlike menopause, POI is not permanent and can be reversed, but it does not mean they cannot necessarily get pregnant anymore or will not menstruate anymore, or that they are now old [2]

POI has been referred to in different terms over time, e.g., premature or early menopause, primary ovarian insufficiency or premature ovarian failure. In this write-up, it will be referred to as POI. The diagnosis of POI requires a minimum of 120 days of amenorrhoea (abnormal absence of menstruation), low levels of estrogen and two reports of high levels of serum Follicle-Stimulating hormone (FSH) of 30-31 days apart. POI is not a strange condition; it is rather a frequent occurrence in 0.01% of all women and 0.001% of women below 30 years [3]. As a consequence of estrogen deficiency, POI causes osteoporosis and cardiovascular disease. Women already in menopause and those who have POI have similar symptoms, but these symptoms, plus loss of fertility, can be heartbreaking for these young individuals [4]. POI generally occurs from abnormal functioning or early decline of the follicle pool. In the case when the ovaries are not functioning properly, there are enough ovarian follicles, but they just do not respond to stimulations for follicles to start the folliculogenesis pathway [4].

POI can be natural, caused by chromosome abnormalities, genetic defects, and autoimmune diseases, or idiopathic or unknown. Some cases are syndromic, accompanied by specific diseases. POI can also be iatrogenic, such as chemotherapy or arise from exposure to viral toxic agents like carbon monoxide. This review highlights the role of oxidative stress in POI and the importance of lifestyle factors, particularly diet, influencing the risk and targeting interventions to reduce or delay its onset.

II. HALLMARKS OF POI

About 5% of all POI cases are autoimmune, while about 15% of the cases are genetic [5]. An increased danger of oxidative stress is most likely the result of genetic anomalies that impede the host's antioxidant protection, DNA repair process and mitochondria. Additionally, oxidative stress could occur from an overreactive immune system. In contrast, iatrogenic POI, caused by radiation and chemotherapy, will increase oxidative stress because of programmed cell death and tissue degradation. The distinguishing features of premature ovarian insufficiency related to genetics, autoimmune conditions and chemotherapy/radiation are discussed below

A. POI GENETIC CAUSES

The result that a first-degree relation is impacted in roughly 10-30% of irreversible cases and that a woman with an impacted mother is six times more likely to get POI backs and support the concept that there is a genetic element to the causes of premature ovarian insufficiency. Several chromosomal irregularities, single gene alterations and changes in genetic forms from many biological mechanisms linked to the development of POI have been found through genetic inquiries of POI patients [6].

B. OESTROGEN AND OXIDATIVE STRESS.

It is commonly known that estrogen has antioxidant qualities. Because of their phenolic ring, they are ROS- ROS-scavenging hormones. Nonetheless, it is believed that women's blood levels of estrogen are too low to directly cause appreciable antioxidant effects [7]. Manganese-superoxide dismutase and glutathione peroxidase are two examples of antioxidant enzymes whose activity can be increased by estrogen. Studies on animals and in experiments have confirmed the antioxidant qualities of estrogen. In vitro studies have demonstrated that the three phenolic estrogens present in mammals, namely estrone, estradiol, and estriol, possess a total antioxidant activity that is 2.5 times greater than that of vitamin C. Lipid peroxidation was much lower in other investigations using estradiol administration in female mice and pigs. Less is known about estrogen's antioxidant effects in humans. Isoprostanes, a biomarker of oxidative stress, were positively correlated with estrogen levels in the BioCycle study, which tracked

reproductive hormone cycles in healthy premenopausal women. The same investigation found a significant correlation between serum estrogen and the antioxidants lutein, tocopherol and ascorbic acid [8]. According to this research, estrogen is a key player in oxidative stress, and fluctuations in estrogen levels may affect fertility.

C. RISK FACTORS FOR POI

DIET

An earlier start of menopause has been linked to increased consumption of vegetarian foods, according to several observational studies. Increased intake of green and yellow vegetables was linked to an earlier onset of natural menopause, according to a systematic review [9]. Additionally, observational studies identified links between the use of soy products and a trend for increasing consumption of cereal, fiber, and vegetables with an increased risk of earlier onset of menopause. Furthermore, in a cross-sectional investigation, it was observed that not being a vegetarian was connected with a later age of natural menopause onset. A more recent study found no correlation between eating a healthy plant-based diet that is healthy and going through menopause before your time. However, an improper plant-based diet may put you at risk. In a similar vein, the UK women's cohort study, a sizable long-term cohort study that tracked 14,172 participants over four years, discovered that eating refined rice and pasta was linked to an earlier natural menopause, while eating fresh legumes was inversely linked to the onset of natural menopause. In addition, research has shown that a higher intake of fruits and a higher intake of vegetable protein were linked to a delay in the natural menopause. The result of observational studies regarding the consumption of plant-based or vegetarian diets and food has produced contradictory findings, some of which can be clarified by studying the mechanism of action. While plant-based diets and food are rich in beneficial polyphenols with antioxidant properties, they are also a source of phytoestrogens. Non-steroidal polyphenolic compounds, or phytoestrogens, are naturally occurring in plants such as legumes, sesame seeds, cereals, nuts and other plants [10]. These compounds are similar to mammalian estrogens, with effects on the reproductive system. They exert their estrogenic effects by binding estrogenic receptors, acting as agonists, partial agonists, and antagonists. A substantial body of research has been done on the benefits of phytoestrogens, including their antioxidant and anti-inflammatory properties. Nonetheless, research on animals has demonstrated that phytoestrogens can impact reproduction.

HIGH FAT DIET

High levels of intracellular fatty acids can affect the structure of the mitochondrial membrane, causing mitochondrial dysfunction. Increased fat consumption can also result in unfavorable physiological conditions in the body [11]. Adipocytes begin to undergo excessive hypertrophy to accommodate excess fat consumption, which increases oxidative stress and endoplasmic reticulum stress. Chronic overnutrition also causes intracellular lipid accumulation in other tissues, which can lead to lipotoxicity, insulin resistance, cellular dysfunction and apoptosis in multiple organs. Oocytes from mice on a high-fat diet have elevated lipid content in their ovaries. Moreover, triglyceride levels in follicular fluid are observed to be higher in obese women. It has been shown that obese women are less likely to become pregnant when using autologous oocytes rather than donor oocytes. This suggests that obesity may have an impact on the quality of oocytes, potentially because of increased lipid content. A high-fat diet caused oocytes in a mouse study to mature later.

Although there have been a few studies directly examining the relationship between dietary fat intake and reproduction in humans, it is most likely linked to altered reproductive function. Menstrual cycle tended to be longer in research, including healthy premenopausal women who followed a 40% fat diet as opposed to a 20% fat diet. In another study, women from South Africa were fed a Western-style diet that included meat, increasing their fat intake by 5% for two months. This led to higher levels of FSH, lower levels of estrogen, and longer follicular phases of their cycles [12]. Therefore, a diet heavy in fat may raise the risk of POI.

BODY MASS INDEX (BMI)

There is a lack of consistent and clear research examining the relationship between BMI and ovarian failure. Body Mass Index (BMI) is a commonly used proxy for adiposity that calculates body fat based on height and weight of the individual. An elevated BMI has been linked to several medical diseases, such as infertility and reproductive issues [13]. There is, however, little evidence linking a high BMI to menopause age and less evidence linking it to POI. Relative Energy Deficiency in Sport (RED-S), which can cause delayed puberty, amenorrhea and other menstrual irregularities, is one reproductive issue that low BMI might cause. There is insufficient data to establish a clear link between malnutrition and early menopause in women, even if it may affect reproductive health. Severe malnutrition, however, causes early menopause or amenorrhea in young women.

Numerous research studies have discovered a weak correlation between being underweight and a later menopausal age and between being overweight and a younger menopausal age. This does seem counter-intuitive given the link between obesity and oxidative stress and inflammation, as well as the potential effects on ovarian function. Furthermore, many studies lack sufficient control to account for the effects of smoking on body weight, even though smoking is known to significantly affect menopause age.

The synthesis of estrone in the adipose tissue of overweight and obese women could be one reason for the association between BMI and menopause age. The enzyme aromatase in adipose tissue transforms circulating androstenedione, which is generated by the adrenal gland and the ovary, into estrone and a weak estrogen. Age and body weight are known to increase the expression and activity of aromatase in adipose tissue. Estrogen is positively correlated with body weight and plays a role in a woman's total estrogen production. This extra estrogen is thought to be a factor in the menopausal delay [13].

The synthesis of leptin in adipose tissue may also be a factor in the relationship between BMI and menopause age. Leptin is involved in the onset of puberty, the regulation of normal reproductive function, and the transmission of information about the body's energy stores to the hypothalamus. Early menopause has been linked to low leptin levels, according to one study. Nevertheless, more research is needed to confirm this link between leptin and menopause age.

There seems to be a direct mechanistic connection between obesity and decreased reproductive function. It is established that being overweight can raise the body's level of oxidative stress via a variety of possible pathways, one of which is an increase in Reactive Oxygen Species (ROS) in adipose tissue. In a similar vein, obesity and persistent low-grade inflammation in the body are linked. It is thought that adipokines, which are produced by adipose tissue, an essential endocrine organ, play a role in inflammation. A good diet, regular exercise, and weight loss are examples of lifestyle changes that can help reduce inflammation and lessen the negative effects of obesity on conditions linked to inflammation [13].

The gut microbiome plays a critical role in reproductive health as well. There is debate over whether the altered gut microbiota is a cause or an effect of obesity, but it is known that obesity alters the composition of the gut bacteria, which triggers an inflammatory response.

EXERCISE

It is acknowledged that a healthy lifestyle includes regular exercise as a key component. Nevertheless, high-intensity exercise produces markers of oxidative stress and elevated cortisol. Moreover, irregular menstrual cycles and ovulation are linked to abruptly increasing intense exercise, especially when combined with low energy availability (RED-S) [14]. These abnormalities, which include shortened luteal phase, decreased progesterone, and elevated cortisol, seem mild. If a woman exercises vigorously and her body weight falls below a certain critical level, she may experience amenorrhea (defined as not having a menstrual cycle for three or more months) in addition to other stressors like illness, calorie restriction, improper eating habits, or psychological stress. On the other hand, exercise seems to help overweight and obese women regain their ovulation.

Although the benefits of exercise for general health and well-being are well established, there does not appear to be any concrete evidence linking exercise to the development of POI. However, the relationship between exercise and a woman's menopausal age appears to be complex, and many other factors are probably at play. There is some limited evidence to support this theory. Research has indicated that women who participate in regular physical activity tend to go through menopause later in life than sedentary women, although other studies have not found any correlation.

D. OTHER LIFESTYLE FACTORS

SMOKING

Research has linked tobacco smoke pollutants to endocrine problems, early menopausal onset, subfertility, and post-op [15]. The early menopausal onset linked to smoking implies a connection to early follicular depletion. According to a meta-analysis, women who smoke have a significantly higher risk of infertility than women who do not smoke. Women's ovarian reserve is decreased, and their oocyte quality is severely harmed by smoking.

PSYCHOLOGICAL STRESS

From experience, a lot of women with POI associate extended periods of pressure or stress with the beginning of ovarian failure; however, there is little evidence to support this association, and the precise mechanisms underlying this relationship are even less clear.

A state of pressure and emotional strain is called stress. Certain degrees of stress may even be considered advantageous, and there's even some proof that they can enhance performance in a variety of contexts. However, persistent or excessive stress can result in health issues like strokes and depression. The hypothalamic-pituitary-adrenal axis, the sympathetic nervous system, and the release of stress hormones like cortisol, adrenaline, and nor-adrenaline are all triggered when a person is in a stressful situation. This is known as the fight-or-flight response. The body may be better equipped to handle stressful situations thanks to these hormones. When a person experiences more emotional strain and pressure than they can manage in a given situation, it can lead to psychological stress. A person's general wellbeing and mental health may be negatively impacted over time by excessive psychological stress, which can result in a variety of behavioral, emotional and physical symptoms.

Similarly, high levels of psychological stress can affect reproductive health by upsetting the body's hormone balance in

the hypothalamic-pituitary-gonadal axis, which may have an impact on folliculogenesis and the menstrual cycle. This condition, which has also been called functional hypothalamic amenorrhea, has several risk factors as well as connections to factors related to stress, weight, and exercise.

Although POI has been linked to depression, anxiety, and other negative emotions, few studies have found a connection between POI and stress. Furthermore, research on chronic unpredictable mild stress in animals revealed that stress could cause depression-like behaviors and a decrease in ovarian reserve in female rats. It is evident that long-term psychological stress appears to be associated with certain outcomes, but more research is needed to assess the relationship between psychological stress and ovarian function to comprehend the mechanisms underlying stress-induced dysfunction [15].

AGING

The ageing of mothers is linked to decreased oocyte quality and quantity. As women age, there is mounting evidence that DNA damage increases and repair mechanisms become less effective [16]. Moreover, a higher rate of miscarriage indicates a correlation between growing female age and aneuploidy, or an uneven chromosomal complement in oocytes [17]. According to a thorough investigation, aneuploidy affects 20% of women's oocytes from the age of 35 to nearly 60% of women's oocytes from the age of 43. Reduced stringency in checkpoints during oocyte meiotic activation and an increase in errors during meiotic cell division in older oocytes are some of the causes of the increased aneuploidy associated with aging. Age-related increases in mitochondrial activity, measured by ATP production and metabolic activity, decrease with maternal age. Older women are linked to higher oxidative stress, which increases their risk of ovarian malfunction and infertility due to increased DNA damage and mitochondrial failure.

E. POTENTIAL DIETARY INTERVENTIONS

Diet is a risk factor for POI, as was previously mentioned. There have been numerous reviews of dietary supplements including single components for POI elsewhere. We highlight some of the possible ways that nutrition, or parts of a diet, may help lower the risk of POI in this section.

MELATONIN

A powerful and adaptable antioxidant supplement, melatonin is a hormone generated by the pineal gland in the brain that controls the sleep-wake cycle. Melatonin has been demonstrated in studies to lessen oxidative stress in a range of organ systems. Less is known, meanwhile, regarding melatonin's antioxidant qualities in the ovary and how they relate to fertility in humans. Melatonin has been shown to increase the developmental competence and quality of oocytes in women, as well as to increase the success of in vitro fertilization (IVF) treatments. Melatonin has also been demonstrated to guard against oxidative stress-induced ovarian tissue damage and may guard against POI, according to mounting data.

Follicle fluid contains high concentrations of melatonin, up to three times that of serum, and the concentration of melatonin rises with follicle growth [18]. The hormone has been proposed to be essential for ovarian health, since oxidative stress can lead to DNA damage in granulosa cells and higher melatonin concentrations in developing follicles. Regarding melatonin and oxidative damage in follicles, different outcomes have been seen in human studies; however, the majority of the research has been conducted on animals. It has been demonstrated that melatonin supplementation significantly reduces intrafollicular DNA damage and has a tendency to lower lipid damage [19].

Numerous studies have demonstrated that melatonin, which is widely used in artificial reproductive technologies (ART), can improve oocyte quality, increase follicular growth rate, increase fertilization rate, and increase the number of quality embryos, all of which can lead to improved pregnancy outcomes [20]. Studies on humans and animals have demonstrated that melatonin enhances oocyte maturation [21]. Three milligrams of melatonin supplementation are found to significantly increase the number of mature oocytes in an 85-patient randomized control trial [22]. Melatonin supplementation was found by Tamura et al. to significantly reduce the number of degenerate oocytes [23].

In order to shield oocytes from the buildup of DNA damage during prophase arrest, melatonin has been demonstrated in mice to improve the repair of double-strand breaks via the non-homologous end joining (NHEJ) pathway [24]. This helps prevent the deterioration of oocyte quality during meiotic maturation. This bears an intriguing resemblance to POI, in which the activation of DNA damage pathways is one of the mechanisms responsible for the early loss of follicles. Furthermore, as previously mentioned, a large number of genes associated with familial POI are involved in DNA damage repair, underscoring the significance of these pathways.

It's interesting to note that melatonin has also been demonstrated to shield the ovaries from harm caused by chemotherapy, which may suggest a significant role in preventing the loss of ovarian follicles too soon. Mice treated with melatonin before being given cyclophosphamide by [25] demonstrated preserved ovarian function [26]. The findings demonstrated that melatonin improved mitochondrial activity, decreased ROS levels in the ovary, and lessened oocyte loss. Further research has demonstrated that melatonin inhibits ovarian granulosa cell apoptosis and maintains anti-Müllerian hormone (AMH) expression, thereby preventing cyclophosphamide-induced over-activation of primordial

follicles [27]. Apoptosis occurs in the activated follicles, leading to POI in the end. However, in contrast, melatonin together with treatment reduced the initiation of initial follicles and the programmed cell death of the granulosa cells that release AMH in growing follicles. This indicates the ovary's cytoprotective advantages of melatonin, and this could provide new methods to protect the ovary's reserve from damage caused by chemotherapy. It is advised for young cancer patients going through chemotherapy to adopt this strategy.

MITOCHONDRIAL-TARGETED NUTRIENT THERAPY

It is believed that oxidative stress as a result of mitochondrial malfunction plays an important role in the danger of premature ovarian insufficiency. Therefore, overproduction of reactive oxygen species can be fought by antioxidants, most especially in women who have a gene alteration related to the mitochondria that results into the development POI [28].

Several studies have recorded the impact of polyphenols found in plants and various antioxidant supplements on mitochondrial activity [29]. Reports have been made that epigallocatechin-3-gallate (EGCG) improves mitochondrial activity. Based on in vitro studies, EGCG hinders oxidative stress-induced programmed cell death in an array of cell lines by way of the mitochondrial pathway [30]. Investigation carried out in vivo showed that EGCG could increase mitochondrial antioxidant enzymes, reduce death of cells through the mitochondrial pathway, and replenish respiration rates in diverse tissues and cells of mammals, the heart and liver included [30]. Moreover, EGCG showed protective outcomes against cigarette smoke-induced mitochondrial dysfunction in rat studies [31]. In relation to the ovaries, EGCG reduced the follicular atresia caused by chemotherapy and triggered the pathways of nuclear factor erythroid2-related factor 2 (Nrf2)/heme oxygenase-1 and superoxide dismutase 2 in mice [32]. Moreover, it has been demonstrated that EGCG quickens the development of diabetic oocytes in mice [33] and bovine oocytes in vitro [33] existing in plants naturally N-acetyl-L-cysteine is a precursor to both the antioxidant glutathione and the amino acid L-cysteine. It's been proven that N-acetyl-l-cysteine enhances mitochondrial function [35]. Nicotinamide mononucleotide (NMN) intake has been proved to slow down oocyte aging [36] and improve oocyte quality in aged mice, which has been connected to mitochondrial function [37]. Furthermore, studies have shown that resveratrol improves mitochondrial function and improves the in vitro development of oocytes from elderly mice and humans [38]. Plants like berries, broccoli, apples, and onions include quercetin, a naturally occurring flavonoid [39]. Quercetin has been proved in studies to scavenge free radicals and activate antioxidant enzymes, thereby preventing mitochondrial dysfunction. Quercetin has been shown in vivo and in vitro to improve oocyte quality and delay ovarian ageing [40]. The method of OXPHOS-mediated ATP synthesis involves electron transfer to ubiquinone, or CoQ10. CoQ10 is an antioxidant that has been proven to deplete with age [41]. It has been proving that including CoQ10 to oocytes from aging female mice causes an increase in mitochondrial activity. The female ovaries in a CoQ10 deficient PDSS-2 mouse model, in which CoQ10 synthesis was disturbed in the mouse oocytes, had no healthy follicles and resembled the circumstances seen in POI. Supplementing with CoQ10 raised superoxide levels and mitochondrial membrane potential while pausing the depletion of ovarian reserve [42]. Even though there are numerous potential antioxidant compounds, it is not known how these compounds will perform as antioxidants in the mitochondria because of their low level of bioavailability.

Over time, more specialized antioxidants have been produced, like BGP-15 and MitoQ. MitoQ is a lipophilic cation-linked ubiquinone moiety that allows the compound to accumulate in the mitochondria. MitoQ drastically reduces nitrotyrosine, a biomarker of protein oxidation, and raises the level of mitochondrial membrane potential, suggesting a possible improvement in mitochondrial function, according to a systematic review of animal studies [43]. BGP-15 is another substance that builds up in mitochondria [44]. In oocytes from obese mice, BGP-15 improves mitochondrial function and mtDNA copy number while also improving oocyte quality [45]. Although these substances possess an affinity for mitochondria, it is not known if they would enter ovarian cells' mitochondria after being ingested. Oxidative stress is stated to decrease in human studies following MitoQ ingestion. Consumption of 20 mg/d of MitoQ for six weeks reduced plasma-oxidized LDL (low-density lipoprotein), a sign of oxidative stress, and heightened age-related vascular function in older adults, according to a study [46]. Studies relating to oxidative stress caused by exercise revealed that a daily dose of 20 mg MitoQ supplementation could considerably lower the concentration of H2O2 in skeletal muscle [47] and post-exercise plasma F2-Isoprostanes oxidants [48], while also protecting nuclear and mitochondrial DNA from harm. Acute 20 mg MitoQ supplementation, however, did not affect male biomarkers of exercise-induced oxidative stress [49]. These exercise studies, though, were limited to men. Patients with peripheral artery disease showed a significant increase in plasma superoxide dismutase, an enzyme important to antioxidant defense, following acute supplementation with MitoQ (80 mg) [50]. Although these human studies indicate that supplementing with MitoQ lowers oxidative stress, no research has examined the function of the ovaries.

OILY FISH

Fish, especially oily fish, is linked to better ovarian health and a postponement of the natural menopause. A high consumption of oily fish was found to increase the age at which menopause began by 3.3 years in a large cohort study [51]. Omega-3 anti-inflammatory fatty acids, especially the polyunsaturated ones eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are found in oily fish. In one study, taking an omega-3 supplement for one month resulted in a significant decrease in

inflammation and a significant decrease in FSH in women of normal weight [52]. Additionally, dietary administration of omega-3 reversed the ovarian decline induced by high-fat diets [53] and enhanced oocyte quality [54] in studies conducted on mice. These two studies point to an omega-3-related role in prolonging reproductive lifespan. *In vitro* studies on human endothelial cells have demonstrated that omega-3 can lessen oxidative stress-induced damage and DNA damage [55]. Additionally, a study demonstrated that endothelial cells' intracellular ROS was significantly decreased by EPA and DHA omega-3s. Omega-3 fatty acids are known to have many health benefits, but fish oil supplements are prone to oxidation [56]. As a result, mixing it with other substances like vitamin E or alpha-lipoic acid may help preserve its therapeutic effectiveness [57]. Moreover, eating fish rather than fish oil is probably more beneficial [58].

DAIRY CONSUMPTION

It has been suggested that dairy products enhance fertility and postpone the natural menopause. Reduced-fat dairy products like yoghurt and skimmed milk have been connected to a reduced risk of early natural menopause, which is defined as the menopause that starts before 45 years [59]. This information comes from the Nurses' Health Study II (NHSII) cohort. In a different cohort study, women who consumed more than three servings of low-fat dairy products went through a 3–6-month delay in the start of natural menopause compared to those who did not [60]. Similarly, consumption of dairy products, milk, and fermented dairy products was linked to a reduced rate of decline in anti-Mullerian hormone (AMH), a sign of ovarian reserve, in a study that followed regularly menstruating women for 16 years. Moreover, the study showed that consumptions of lactose and free galactose were also connected to a smaller yearly decline in AMH [61]. A recent study that demonstrated a high intake of galactose and lactose was connected to a later onset of natural menopause in Japanese women [62] reinforced this even more.

Antioxidant effects of milk and dairy products are well established [63]. Antioxidant compounds found in milk and milk-derived products include β-carotene, vitamins A, C, and E, as well as the proteins whey and casein. Antioxidant ability was proven for each of the casein subunits [64]. Furthermore, a few of the biopeptides formed during casein digestion have antioxidant qualities [65]. Moreover, milk's whey component has antioxidant qualities; in particular, it is a source of cysteine amino acids, a substrate for the production of glutathione, a vital antioxidant in the body. The most potent antioxidant in dairy products and milk fat is believed to be conjugated linoleic acid (CLA) [66]. It has been demonstrated that CLA scavenges free radicals in vitro [67] and decreases lipid oxidation in vivo [68]. The well-known antioxidants in milk and dairy products may play a significant part in lessening ovarian damage and dysfunction, which in turn lowers the risk of POI.

Products made from dairy can alter gut microbiota. The primary source of "milk sugar," lactose, which is hydrolyzed into glucose and galactose, is milk and milk-derived products. Studies conducted on animals and in vitro have shown that lactose promotes the growth of Lactobacillus and Bifidobacterium [69] and is regarded as a prebiotic. Lactose can be used by Lactobacillus and Bifidobacterium to produce anti-inflammatory short-chain fatty acids, primarily butyrate, propionate, and acetate [70]. Additionally, probiotics found in fermentable dairy products like yoghurt can slow the growth of harmful bacterial strains like Bacteroides fragilis in the gut [70].

Dairy consumption offers advantages, but it's crucial to remember that ovarian toxicity can result from galactose buildup. Galactose-1-phosphate uridyl transferase is the enzyme that breaks down galactose; galactosemia is a condition that affects women. Women who have low or no activity of the enzyme are more likely to experience menopause and ovarian failure early in life [70]. Furthermore, a high galactose diet may encourage menopause in the general population [71].

When considered collectively, the data point to the possibility that dairy consumption may lengthen reproductive life expectancy through effects on gut microbiota and antioxidants. Since AMH is a more accurate indicator of decreased ovarian reserve than FSH, it has been favorably evaluated for use in POI diagnosis [72]. Dairy may play a part in lowering the risk of POI since it has been demonstrated to affect AMH levels in premenopausal women. It will be especially important for women with autoimmune diseases or high body mass index who also experience disruptions in their gut microbiome. Conversely, consuming dairy products in their whole form may raise fat intake, which may raise oxidative stress and reduce the health benefits of dairy. Cohort studies have demonstrated a specific correlation between low-fat dairy consumption and a postponement of the natural menopause. It is noteworthy that milk fat comprises a multitude of antioxidant compounds, including CLA and lipophilic antioxidants like vitamin A and β-carotene. Consequently, one may need to consider other factors, such as BMI, when deciding whether to consume full-fat or low-fat dairy. In addition, care must be exercised when consuming a lot of dairy products because they can cause galactose to build up. Women who have galactosemia or lactose intolerance may also find it inappropriate to consume dairy products.

VITAMIN C AND E

One well-known natural antioxidant is ascorbic acid (AA), also known as water-soluble vitamin C (reviewed in detail elsewhere). In women with luteal phase defects, supplementation with AA was demonstrated to increase progesterone and pregnancy success, indicating a potential role during heavy exercise-induced disruptions to ovulation [73]. AA was able to stop the ovarian ageing effects in aging female

mice, which included granulosa cells, ovarian follicle number, and ovarian volume reduction. Supplementing vitamin C may also help lessen the oxidative damage that electromagnetic radiation (EMR) causes. Rats exposed to EMR were shown to exhibit a significant reduction in oxidative stress-induced apoptosis following oral administration of vitamin C [74]. Nevertheless, vitamin C also decreased serum AMH in the same investigation

Regarding POI, vitamin C appears to have promising effects. Women's psychological stress and oxidative stress brought on by exercise are risk factors for POI that can be mitigated by vitamin C [75]. A mouse model of PI was shown to have improved ovarian function when human amniotic epithelial cells treated with vitamin C were transplanted into their ovaries [76].

Tocopherols are a class of compounds that make up vitamin E, with α-tocopherol being the form that humans absorb the most of. The antioxidant properties of α-tocopherol in ovarian tissue and follicular fluid are widely recognized. Furthermore, women with POI have much lower levels of α-tocopherol than women with regular menstrual cycles [77].

III. CONCLUSION

Modified lifestyles tailored to the genetic makeup of women with POI show significant promise. At the moment, it appears that the genes linked to POI are involved in several important biological processes, including folliculogenesis, energy and metabolism, meiosis/DNA damage repair, and sex steroid metabolism. Understanding their genetic background allows for the adaptation of specific lifestyle modifications, like diet and exercise regimen, to meet their specific needs and either prevent or delay the onset of POI or lessen its symptoms for better management. Lifestyle modifications that lower oxidative stress and inflammation and address specific nutrient deficiencies may improve outcomes for women with POI, even though there may be a complex and overlapping pattern of mechanisms related to genetic background. These changes may also delay the age at which those who are genetically predisposed to menopause begin to experience symptoms, as we have observed in women who are menopausal naturally and those who have undergone chemical or surgical menopause.

IV. ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors.

V. RESEARCH INVOLVING PLANTS

Not applicable.

VI. CONSENT FOR PUBLICATION

Not applicable.

VII. CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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NOT APPLICABLE

REFERENCES

[1] M. De Vos, P. Devroey, B.C. Fauser, **"**Primary ovarian insufficiency". *Lancet***, 2010**, *376*, 911–921.
[2] A. Cano, "*Menopause: A Comprehensive Approach"*; Springer: Cham, Switzerland, **2017**.
[3] A.N. Shelling, "Premature ovarian failure". *Reproduction*, **2010**, *140*, 633
[4] O. A. Ojo, P. I. Nwafor-Ezeh, D. E. Rotimi, M. Iyobhebhe, A. D. Ogunlakin, and A. B. Ojo, "Apoptosis, inflammation, and oxidative stress in infertility: A mini review", *Toxicology Reports*, **2023**, *10*, 448-462.
[5] D. Tiosano, J.A. Mears, D.A. Buchner, "Mitochondrial dysfunction in primary ovarian insufficiency". *Endocrinology*, **2019,** *160*, 2353–2366.
[6] C. Chapman, L. Cree, A.N. Shellin, The genetics of premature ovarian failure: current perspectives. *Int. J. Womens Health*, **2015**, 7 799–810. 10.2147/IJWH.S64024
[7] C. Borrás, J. Gambini, M.C. Gómez-Cabrera, J. Sastre, F.V. Pallardó, G.E. Mann, J. Viña, "17β-oestradiol up-regulates longevity-related, antioxidant enzyme expression via the ERK1 and ERK2 [MAPK]/NFκB cascade". *Aging Cell*,**2005 ,***4*, 113–118.
[8] S.L. Mumford, R.W. Browne, K.C. Schliep, J. Schmelzer, T.C. Plowden, K.A. Michels, L.A. Sjaarda, S.M. Zarek, N.J. Perkins, L.C. Messer, "Serum antioxidants are associated with serum reproductive hormones and ovulation among healthy women". *J. Nutr.*,**2016,** *146*, 98–106.
[9] G. Grisotto, J.S. Farago, P.E. Taneri, F. Wehrli, Z.M. Roa-Díaz, B. Minder, M. Glisic, V. Gonzalez-Jaramillo, T. Voortman, P. Marques-Vidal, **"**Dietary factors and onset of natural menopause: A systematic review and meta-analysis". *Maturitas*,**2022**, *159*, 15–32.
[10] M. Mostrom, T.J. Evans, "Phytoestrogens. In *Reproductive and Developmental Toxicology*; Elsevier: Amsterdam, The Netherlands", **2011**, pp. 707–722.
[11] R.L. Robker, L.K. Akison, B.D. Bennett, P.N. Thrupp, L.R. Chura, D.L. Russell, M. Lane, R.J. Norman, "Obese women exhibit differences in ovarian metabolites, hormones, and gene expression compared with moderate-weight women". *J. Clin. Endocrinol. Metab.**2009***, , *94*, 1533–1540.
[12] C.K. Welt, Y.L. Pagan, P.C. Smith, K.B. Rado, J.E. Hall, Control of follicle-stimulating hormone by estradiol and the inhibins: critical role of estradiol at the hypothalamus during the luteal-follicular transition. J Clin Endocrinol Metab. **2003**, 8(4):1766-71.
[13] R. O. Arise et al., "Kinetics of angiotensin-1 converting enzyme inhibition and antioxidative properties of Azadirachta indica seed protein hydrolysates", *Heliyon*, 2019, *5*.
[14] O. Hakimi, L.C. Cameron, Effect of Exercise on Ovulation: A Systematic Review. Sports Med. **2017,** 47(8):1555-1567.
[15] G.G. Collins, B.V. Rossi, "The impact of lifestyle modifications, diet, and vitamin supplementation on natural fertility". *Fertil. Res. Pract*, **2015**, *1*, 11.
[16] M. Maidarti, R.A. Anderson, E.E. Telfer, "Crosstalk between PTEN/PI3K/Akt signaling and DNA damage in the oocyte: Implications for primordial follicle activation, oocyte quality and ageing". *Cells*, **2020,** *9*, 200.
[17] Brossens *et al*., 2022
[18] A. Brzezinski, M.M. Seibel, H.J. Lynch, M.H. Deng, R.J. Wurtman, "Melatonin in human preovulatory follicular fluid". *J. Clin. Endocrinol. Metab.*, **1987**,*64*, 865–867.
[19] H. Tamura, A. Takasaki, T. Taketani, M. Tanabe, F. Kizuka, L. Lee, I. Tamura, R. Maekawa, H. Asada, Y. Yamagata N. Sugino, "Melatonin and female reproduction." *J. Obstet. Gynaecol. Res.*, **2014**, *40*, 1–11.
[20] H. Tamura, A. Takasaki, T. Taketani, M. Tanabe, F. Kizuka, L. Lee, I. Tamura, R. Maekawa, H. Asada, Y. Yamagata, "Melatonin as a free radical scavenger in the ovarian follicle". *Endocr. J.*, **2013**, *60*, 1–13.

[21] A.S. Batıoğlu, U. Şahin, B. Gürlek, N. Öztürk, E. Ünsal, **"**The efficacy of melatonin administration on oocyte quality". *Gynecol. Endocrinol*, **2012**, *28*, 91–93.
[22] J. Leem, G.Y. Bai, J.S. Kim, J.S. Oh, "Melatonin protects mouse oocytes from DNA damage by enhancing nonhomologous end-joining repair". *J. Pineal Res*, **2019**, *67*, e12603.
[23] H. Tamura, A. Takasaki, I. Miwa, K. Taniguchi, R. Maekawa, H. Asada, T. Taketani, A. Matsuoka, Y. Yamagata, K. Shimamura, H. Morioka, H. Ishikawa, R.J. Reiter, N. Sugino, Oxidative stress impairs oocyte quality and melatonin protects oocytes from free radical damage and improves fertilization rate. J Pineal Res. **2008**, 44(3):280-7.
[24] R.S. Barberino, V.G. Menezes, A.E.A.S. Ribeiro, R.C. Palheta, X. Jiang, J.E.J. Smitz, M.H.T. Matos, Melatonin protects against cisplatin-induced ovarian damage in mice via the MT1 receptor and antioxidant activity, Biol. Reprod. **2017**, 96: 1244–1255
[25] J. Feng, W.M. Ma, H.X. Li, X.Y. Pei, S.L. Deng, H. Jia, W.Z. Ma, "Melatonin prevents cyclophosphamide-induced primordial follicle loss by inhibiting ovarian granulosa cell apoptosis and maintaining AMH expression". *Front. Endocrinol.*, **2022**, *13*, 895095.
[26] D. Tiosano, J.A. Mears, D.A. Buchner, "Mitochondrial dysfunction in primary ovarian insufficiency". *Endocrinology*, **2019,** *160*, 2353–2366.
[27] M. Fiorani, A. Guidarelli, O. Cantoni, "Mitochondrial reactive oxygen species: The effects of mitochondrial ascorbic acid vs. untargeted and mitochondria-targeted antioxidants". *Int. J. Radiat. Biol.*, **2021**, *97*, 1055–1062.
[28] M.R. de Oliveira, S.F. Nabavi, M. Daglia, L. Rastrelli, S.M. Nabavi, S.M. "Epigallocatechin gallate and mitochondria—A story of life and death". *Pharmacol. Res*, **2016**, *104*, 70–85.
[29] G. Adikesavan, M.M. Vinayagam, L.A. Abdulrahman, T. Chinnasamy, (-)-Epigallocatechin-gallate (EGCG) stabilize the mitochondrial enzymes and inhibits the apoptosis in cigarette smoke-induced myocardial dysfunction in rats. Mol Biol Rep. **2013**, 40(12):6533-45.
[30] M. Chen, H. Jiang, C. Zhang,"Selected Genetic Factors Associated with Primary Ovarian Insufficiency". *Int. J. Mol. Sci.*,**2023**, *24*, 4423.
[31] S. Chao, L.J. Li, J. Lu, S.X. Zhao, M.H. Zhao, G.A. Huang, S. Yin, W. Shen, Q.Y. Sun, Y. Zhao, "Epigallocatechin gallate improves the quality of diabetic oocytes". *Biomed. Pharmacotherx*, **2018,** *159*, 114267
[32] K. Sahin, M. Tuzcu, H. Gencoglu, A. Dogukan, M. Timurkan, N. Sahin, A. Aslan, O. Kucuk, Epigallocatechin-3-gallate activates Nrf2/HO-1 signaling pathway in cisplatin-induced nephrotoxicity in rats. Life Sci. **2010**, 87(7-8):240-5.
[33] Xiao, H.; Wu, M.; Shao, F.; Guan, G.; Huang, B.; Tan, B.; Yin, Y. (2018). N-Acetyl-L-cysteine protects the enterocyte against oxidative damage by modulation of mitochondrial function. *Mediat. Inflammx*, ***2016,*** 8364279.
[34] Y. Wang, L. Li, L.H. Fan, Y. Jing, J. Li, Y.C. Ouyang, Z.B. Wang, Y. Hou, Q.Y. Sun, "N-acetyl-L-cysteine (NAC) delays post-ovulatory oocyte aging in mouse". *Aging*, **2019**, *11*, 2020.
[35] M.J. Bertoldo, D.R. Listijono, W.-H.J, Ho, A.H. Riepsamen, D.M. Goss, D. Richani, X.L. Jin, S. Mahbub, J.M. Campbell, A. Habibalahi, "NAD+ repletion rescues female fertility during reproductive aging. *Cell Rep.*, **2020**, *30*, 1670–1681.e7.
[36] J. Liu, M. Liu, X. Ye, K. Liu, J. Huang, L. Wang, G. Ji, N. Liu, X. Tang, J.M. Baltz, "Delay in oocyte aging in mice by the antioxidant N-acetyl-L-cysteine (NAC)" *Hum. Reprod.*, **2012,** *27*, 1411–1420.
[37] M. Andreucci, T. Faga, A. Pisani, R. Serra, D. Russo, G. De Sarro, A. Michael, **"**Quercetin protects against radiocontrast medium toxicity in human renal proximal tubular cells" . *J. Cell. Physiol.*, **2018**, *233*, 4116–4125.
[38] M.R. de Oliveira, S.F. Nabavi, M. Daglia, L. Rastrelli, S.M. Nabavi, S.M. "Epigallocatechin gallate and mitochondria—A story of life and death". *Pharmacol. Res*, **2016**, *104*, 70–85.
[39] A. A. Akinduko, S. O. Salawu, A. C. Akinmoladun, A. A. Akindahunsi, and O. O. Osemwegie, "Assessment of the anxiolytic, antidepressant, and antioxidant potential of *Parquetina nigrescens* (Afzel.) Bullock in Wistar rats", *J. Ethnopharmacol*, 2024, *322*, 117597.
[40] A. Ben-Meir, E. Burstein, A. Borrego-Alvarez, J. Chong, E. Wong, T. Yavorska, T. Naranian, M. Chi, Y. Wang, Y. Bentov, **"**Coenzyme Q10 restores oocyte mitochondrial function and fertility during reproductive aging". *Aging Cell*, **2015**, *14*, 887–895.
[41] A.J. Braakhuis, R. Nagulan, V. Somerville, "The effect of MitoQ on aging-related biomarkers: A systematic review and meta-analysis". *Oxidative Med. Cell. Longev.*, ***2018***, 8575263.
[42] K. Sumegi, K. Fekete, C. Antus, B. Debreceni, E. Hocsak, F. Jr Gallyas, F., B. Sumegi, A. Szabo, "BGP-15 protects against oxidative stress-or lipopolysaccharide-induced mitochondrial destabilization and reduces mitochondrial production of reactive oxygen species". *PLoS ONE*, **2017**, *12*, e0169372.
[43] L.L. Wu, D.L. Russell, S.L. Wong, M. Chen, T.S. Tsai, J.C. St John, R.J. Norman, M.A. Febbraio, J. Carroll, R.L. Robker, "Mitochondrial dysfunction in oocytes of obese mothers: Transmission to offspring and reversal by pharmacological endoplasmic reticulum stress inhibitors". *Development*, **2020**, *142*, 681–691.
[44] M.J. Rossman, J.R. Santos-Parker, C.A. Steward, N.Z. Bispham, L.M. Cuevas, H.L. Rosenberg, K.A. Woodward, M. Chonchol, R.A. Gioscia-Ryan, M.P. Murphy, "Chronic supplementation with a mitochondrial antioxidant (MitoQ) improves vascular function in healthy older adults". *Hypertension*, **2018,** *71*, 1056–1063.
[45] D.V. Pham, P.H. Park, Recent insights on modulation of inflammasomes by adipokines: a critical event for the pathogenesis of obesity and metabolism-associated diseases. Arch Pharm Res. **2020**, 43(10):997-1016.
[46] S. Broome, A. Braakhuis, C.J. Mitchell, T. Merry,**"**Mitochondria-targeted antioxidant supplementation improves 8 km time trial performance in middle-aged trained male cyclists". *J. Int. Soc. Sports Nutr.***, 2021**, *18*, 58.
[47] J. Williamson, C.M. Hughes, J.N. Cobley, G.W. Davison, "The mitochondria-targeted antioxidant MitoQ, attenuates exercise-induced mitochondrial DNA damage". *Redox Biol.*, **2020**, *36*, 101673.
[48] S.Y. Park, E.J. Pekas, R.J. Headid, W.M. 3rd; Son, T.K. Wooden, J. Song, G. Layec, S.K. Yadav, P.K. Mishra, I.I. Pipinos, "Acute mitochondrial antioxidant intake improves endothelial function, antioxidant enzyme activity, and exercise tolerance in patients with peripheral artery disease". *Am. J. Physiol.-Heart Circ. Physiol.*, **2020**, *319*, H456–H467.
[49] Y. Dunneram, D.C. Greenwood, V.J.Burley, J.E. Cade, "Dietary intake and age at natural menopause: Results from the UK Women's Cohort Study". *J. Epidemiol. Community Health*, **2017**, *72*, 733–740.
[50] Z.A. Al-Safi, H. Liu, N.E. Carlson, J. Chosich, M. Harris, A.P. Bradford, C. Robledo, R.H. Eckel, A.J. Polotsky, "Omega-3 fatty acid supplementation lowers serum FSH in normal weight but not obese women". *J. Clin. Endocrinol*, **2016**,*101*, 324–333.
[51] N.M. Hohos, E.M. Elliott, K.J. Cho, I.S. Lin, M.C. Rudolph, M.E. Skaznik-Wikiel, **"**High-fat diet-induced dysregulation of ovarian gene expression is restored with chronic omega-3 fatty acid supplementation". *Mol. Cell. Endocrinol.* **x**, **2012**, *499*, 110615.
[52] D. Nehra, H.D. Le, E.M. Fallon, S.J. Carlson, D. Woods, Y.A. White, A.H. Pan, L. Guo, S.J. Rodig, J.L. Tilly, "Prolonging the female reproductive lifespan and improving egg quality with dietary omega-3 fatty acids". *Aging Cell*,**2012**, *11*, 1046–1054.
[53] C. Sakai, M. Ishida, H. Ohba, H. Yamashita, H. Uchida, M. Yoshizumi, T. Ishida, "Fish oil omega-3 polyunsaturated fatty acids attenuate oxidative stress-induced DNA damage in vascular endothelial cells". *PLoS ONE* **x**, **2012**, *12*, e0187934.
[54] B.B. Albert, J.G. Derraik, D. Cameron-Smith, P.L. Hofman, S. Tumanov, S.G. Villas-Boas, M.L. Garg, W.S. Cutfield, "Fish oil supplements in New Zealand are highly oxidized and do not meet label content of n-3 PUFA". *Sci. Rep.* **x**,**2016,** *5*, 07928.
[55] D.V..Nair, M.U. Rani, A.G. Reddy, B.K. Kumar, M.A. Reddy, M. Lakshman, U. Rajkumar, "Protective effect of alpha-lipoic acid and omega-3 fatty acids against cyclophosphamide-induced ovarian toxicity in rats". *Vet. World*, **2020**, *13*, 188
[56]] N. Ahmed Nasef, X. Zhu, M. Golding, A. Dave, A. Ali, H. Singh, G. Garg, "Salmon food matrix influences digestion and bioavailability of long-chain omega-3 polyunsaturated fatty acids". *Food Funct.*, **2021**, *12*, 6588–6602.
[57] A.C. Purdue-Smithe, B.W. Whitcomb, J.E. Manson, S.E. Hankinson, B.A. Rosner, L.M. Troy, E.R. Bertone-Johnson, "A prospective study of dairy-food intake and early menopause". *Am. J. Epidemiol.*, **2019**, *188*, 188–196.
[58] J.L. Carwile, W.C. Willett, K.B. Michels, "Consumption of low-fat dairy products may delay natural menopause". *J. Nutr.*, **2013**, *143*, 1642–1650.

[59] N. Moslehi, P. Mirmiran, F. Azizi, F.R. Tehrani, "Do dietary intakes influence the rate of decline in anti-Mullerian hormone among eumenorrheic women? A population-based prospective investigation". *Nutr. J.*, **2019**, *18*, 83.
[60] M. Yamakawa, K. Wada, Y. Nakashima, C. Nagata, "Dietary lactose and galactose intakes are associated with a later onset of natural menopause among women in a Japanese community". *Br. J. Nutr*, **2023**,*129*, 1607–1614.
[61] I.T. Khan, M. Nadeem, M. Imran, R. Ullah, M. Ajmal, M.H. Jaspal, "Antioxidant properties of Milk and dairy products: A comprehensive review of the current knowledge". *Lipids Health Dis.*, **2019**, *18*, 41.
[62] G. Cervato, R. Cazzola, B. Cestaro, "Studies on the antioxidant activity of milk caseins". *Int. J. Food Sci. Nutr.*, **1999**, *50*, 291–296.
[63] A. Zulueta, M.J. Esteve, A. Frigola, ORAC and TEAC assays comparison to measure the antioxidant capacity of food products. Food Chemistry, **2009**, 114, 310–316
[64] C. Grażyna, C. Hanna, A. Adam, B.M. Magdalena, "Natural antioxidants in milk and dairy products". *Int. J. Dairy Technol*, **2017**, *70*, 165–178.
[65] A. Ali, S. Mehta, C. Starck, M. Wong, W.J. O'Brien, C. Haswell, W. McNabb, K. Rutherfurd-Markwick, N. Ahmed Nasef, "Effect of SunGold Kiwifruit and Vitamin C Consumption on Ameliorating Exercise-Induced Stress Response in Women". *Mol. Nutr. Food Res.*, **2021**, *65*, 2001219.
[66] H.K. Kim, S.R. Kim, J.Y. Ahn, I.J. Cho, C.S. Yoon, T.Y. Ha, "Dietary conjugated linoleic acid reduces lipid peroxidation by increasing oxidative stability in rats". *J. Nutr. Sci. Vitaminol*, **2005**, *51*, 8–15.
[67] H.A. Mäkivuokko, M.T. Saarinen, A.C. Ouwehand, N.E. Rautonen, "Effects of lactose on colon microbial community structure and function in a four-stage semi-continuous culture system". *Biosci. Biotechnol. Biochem.*, **2006**, *70*, 2056–2063.
[68] S. He, H. Li, Z. Yu, F. Zhang, S. Liang, H. Liu, H. Chen, M. Lü, "The gut microbiome and sex hormone-related diseases". *Front. Microbiol.*, **2021**, *12*, 2699.
[69] H. Aslam, W. Marx, T. Rocks, A. Loughman, V. Chandrasekaran, A. Ruusunen, S.L. Dawson, M. West, E. Mullarkey, J.A. Pasco, "The effects of dairy and dairy derivatives on the gut microbiota: A systematic literature review". *Gut Microbes*,**2020,** *12*, 1799533.
[70] D.W. Cramer, B.L. Harlow, W.C. Willett, W.R. Welch, D.A. Bell, R.E. Scully, W.G. Ng, R.C. Knapp, Galactose consumption and metabolism in relation to the risk of ovarian cancer. Lancet. **1989,** 2(8654):66-71
[71] G.S. Cooper, B.S. Hulka, D.D. Baird, D.A. Savitz, C.L., Jr. Hughes, C.R. Weinberg, R.A. Coleman, J.M. Shields, "Galactose consumption, metabolism, and follicle-stimulating hormone concentrations in women of late reproductive age". *Fertil. Steril.*,**1994**, *62*, 1168–1175.
[72] C. Kunt, G. Ozaksit, R. Keskin Kurt, A.N. Cakir Gungor, M. Kanat-Pektas, S. Kilic, A. Dede, "Anti-Mullerian hormone is a better marker than inhibin B, follicle stimulating hormone, estradiol or antral follicle count in predicting the outcome of in vitro fertilization". *Arch. Gynecol. Obstet.*, **2011**, *283*, 1415–1421.
[73] H. Henmi, T. Endo, Y. Kitajima, K. Manase, H. Hata, R. Kudo, "Effects of ascorbic acid supplementation on serum progesterone levels in patients with a luteal phase defect". *Fertil. Steril.*, **2003,** *80*, 459–461.
[74] M. Saygin, O. Ozmen, O. Erol, H.Y. Ellidag, I. Ilhan, R. Aslankoc, "The impact of electromagnetic radiation (2.45 GHz, Wi-Fi) on the female reproductive system: The role of vitamin C". *Toxicol. Ind. Health*, **2018**, *34*, 620–630.
[75] A. Ali, S. Mehta, C. Starck, M. Wong, W.J. O'Brien, C. Haswell, W. McNabb, K. Rutherfurd-Markwick, N. Ahmed Nasef, "Effect of SunGold Kiwifruit and Vitamin C Consumption on Ameliorating Exercise-Induced Stress Response in Women". *Mol. Nutr. Food Res.*, **2021**, *65*, 2001219.
[76] S. Hou, C. Ding, H. Shen, C. Qian, Q. Zou, J. Lu, B. Huang, J. Tan, H. Li, "Vitamin C improves the therapeutic potential of human amniotic epithelial cells in premature ovarian insufficiency disease". *Stem Cell Res. Ther.*, **2020,** *11*, 159.
[77] L. Ma, G. Chen, W. Xu, P. Chen, Y. Lan, Y. Huang, C. Li, J. Zhou, "The relationship between vitamin E level and premature ovarian insufficiency". *J. Obstet. Gynaecol. Res.*, **2021,** *47*, 1481–1486.