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Female Infertility and the Mediterranean Diet

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Abstract

The World Health Organization defines infertility, which affects 80 million women worldwide, as the absence of clinical pregnancy after a year of unprotected and frequent sexual activity. Other variables that affect female infertility include environmental factors, lifestyle choices, and diseases that affect the pathophysiology of the reproductive organs. The impact of alternative therapies is growing in order to support environmental and lifestyle impacts and improve the likelihood of clinical pregnancy in infertile couples. Among alternative treatments, lifestyle modifications including exercise and dietary changes are most prominent. There is currently no essential nutrient or diet for optimizing reproductive health. One of the most extensively studied topics in infertility as well as in many other health issues is the Mediterranean diet. The Mediterranean diet is known for its high intake of fruits, vegetables, whole grains, legumes, oilseeds, and olives as well as its moderate consumption of milk, dairy products, and fish. Olive oil is preferred as the main source of dietary fat in the diet. The diet allows for modest wine consumption as well as less red meat and poultry. The Mediterranean diet's potential impacts on female reproductive health are discussed in this review due to its great nutritional diversity, which includes bioactive ingredients, fiber, and poly- and monounsaturated fatty acids.

1. Introduction

Female infertility refers to infertility caused primarily by female factors such as ovarian reserve decline and ovulation problems. Women with primary female infertility have never given birth, whereas those with secondary female infertility have given birth to a live child or experienced a miscarriage but are unable to become pregnant clinically. In addition to physiological factors, female fertility is influenced by a variety of other factors, including lifestyle. Endometriosis, abnormal ovarian function, tubal infections, and cervical and uterine factors are the most common reproductive diseases, while some cases of female infertility have idiopathic causes (Silvestris, de Pergola, Rosania, Loverro, 2018).

Age, smoking, drinking, being overweight or obese, performing too much or too little exercise, malnutrition or an unbalanced diet, and other health issues are all lifestyle factors linked to infertility outcomes. The first line of defense in treating infertility is to modify relevant lifestyle factors (Rossi, Abusief, Missmer, 2016). Food groups, nutrients, and dietary patterns are all viewed as modifiable lifestyle factors, and evidence for the link between nutrition and infertility is growing by the day.

Recently, there has been increased interest in the relationship between the Mediterranean diet and infertility. Biochemical pregnancy outcomes were positively correlated with Mediterranean diet adherence a research with 161 couples undergoing IVF in the Netherlands. Individuals were assigned a compliance score based on their responses to the food intake frequency questionnaire, and the couple's compliance with the Mediterranean diet was rated as average (Vujkovic et al., 2010). In a study conducted in China, clinical pregnancy rates of high and poor adherence to the Mediterranean diet were 42.62% and 50.94%, respectively. Biochemical pregnancy rates were 27.97% and 31.75%, respectively (Sun et al., 2019). In a case-control study conducted in Spain, higher Western diet adherence was not linked to fertility, but higher Mediterranean diet adherence was associated with improved fertility outcomes (Toledo et al.,2011). The findings of existing studies on the effect of adhering to the Mediterranean diet based on individual consumption on outcomes of assisted reproductive therapy are conflicting due to methodological .

Food groups, nutrients, and various dietary patterns are viewed as modifiable lifestyle factors, and there is mounting evidence that there is a connection between nutrition and infertility. The Mediterranean diet plays a significant role in many different health conditions, including infertility. Therefore, the potential effects of the biochemical components of the Mediterranean diet on the health of female reproduction will be discussed in this paper.

2. Mediterranean Diet

The Mediterranean diet emerged as a dietary pattern in the mid-twentieth century and has since become a worldwide research topic. The current Mediterranean diet pyramid, released in 2010 by the Mediterranean Diet Foundation Expert Group, includes foods that must be consumed at each meal, every day, and once a week as shown in Figure 1 (Bach-Faig, 2011).

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The Mediterranean diet offers a rich variety of nutrients and is an adequate and balanced diet specific to the individual. A high intake of plant-based foods including olive oil, vegetables, fruits, whole grains, legumes, nuts, and olives, as well as a moderate intake of dairy and seafood, define the Mediterranean diet. Additionally, consuming white and red meat and drinking wine in moderation is advised. The antioxidant, vitamin, mineral, and bioactive component composition of the diet is also influenced by whole grain products, legumes, fiber-rich vegetables, and fruits (Lăcătușu, Grigorescu, Floria, Onofriescu, Mihai, 2019). Additionally, eating fish and using olive oil as the primary source of fat in the diet help to balance the diet's fatty acid composition. The Mediterranean diet includes all of these foods, which together contribute to the synergistic benefits of nutrients on health (Skoracka, Ratajczak, Rychte, Dobrowolska, Krela-Kaźmierczak, 2021).

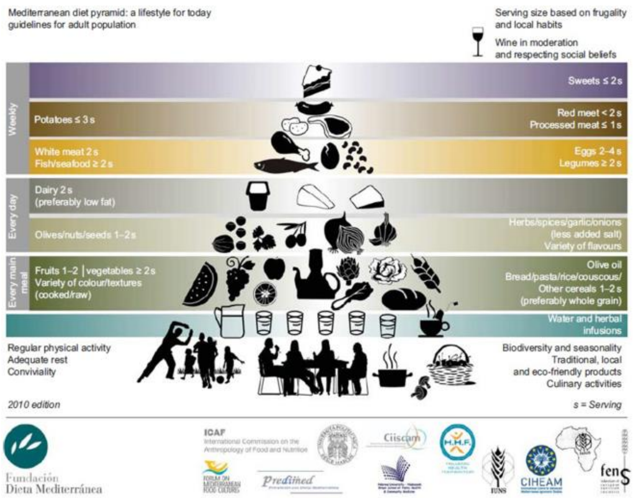

Figure 1. Mediterranean diet pyramid (Bach-Faig, 2011)

The potential effects of Mediterranean Diet components —including bioactive elements, fiber, and mono- and polyunsaturated fatty acids— on female reproductive health will be detailed in the subsequent sections.

2.1. Bioactive ingredients

Bioactive substances are substances with biological and physiological activities that offer health advantages above and beyond the fundamental nutritional value of a food. Polyphenols or polyhydroxyphenols, a considerable class of naturally occurring chemicals having two or more phenol units, make up phenolic compounds. They serve as a plant's defense mechanism against many different environmental challenges, including infections, ultraviolet rays, radiation, and drought (Sanches-Silva et al., 2020). According to the subgroups in their chemical structures, phenolic compounds vary. The main categories are phenolic acids, flavonoids, tannins, carotenoids, stilbenes, lignans, alaloids, avenanthramides, terpenes, and terpenoids. Figure 2 presents the bioactive components as well as their dietary sources. These compounds are abundant in key components of the Mediterranean diet, including vegetables, fruits, grains, legumes, and nuts (Nooshkam, Varidi, Verma, 2020).

Studies on bioactive substances and their effects on health typically focus on their anti-inflammatory and antioxidant capacities.

The presence of one or more phenolic groups reduces reactive oxygen species and many organic substrates while also providing antioxidant properties (Williamson, Holst, 2008). They are critical components of female reproductive health, such as follicular development, ovulation, hormone synthesis, fertilization, embryonic growth, and

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successful implantation. The increase in the release of reactive oxygen species and the deterioration of the antioxidant defense system result in increased oxidative stress. DNA methylation, which can occur as a result of oxidative stress, may have an effect on reproductive potential (Ferroni et al., 2018). As a result, adequate protection against oxidative damage appears to be critical. Some bioactive substances have been shown to alter the effectiveness of the female reproductive system.

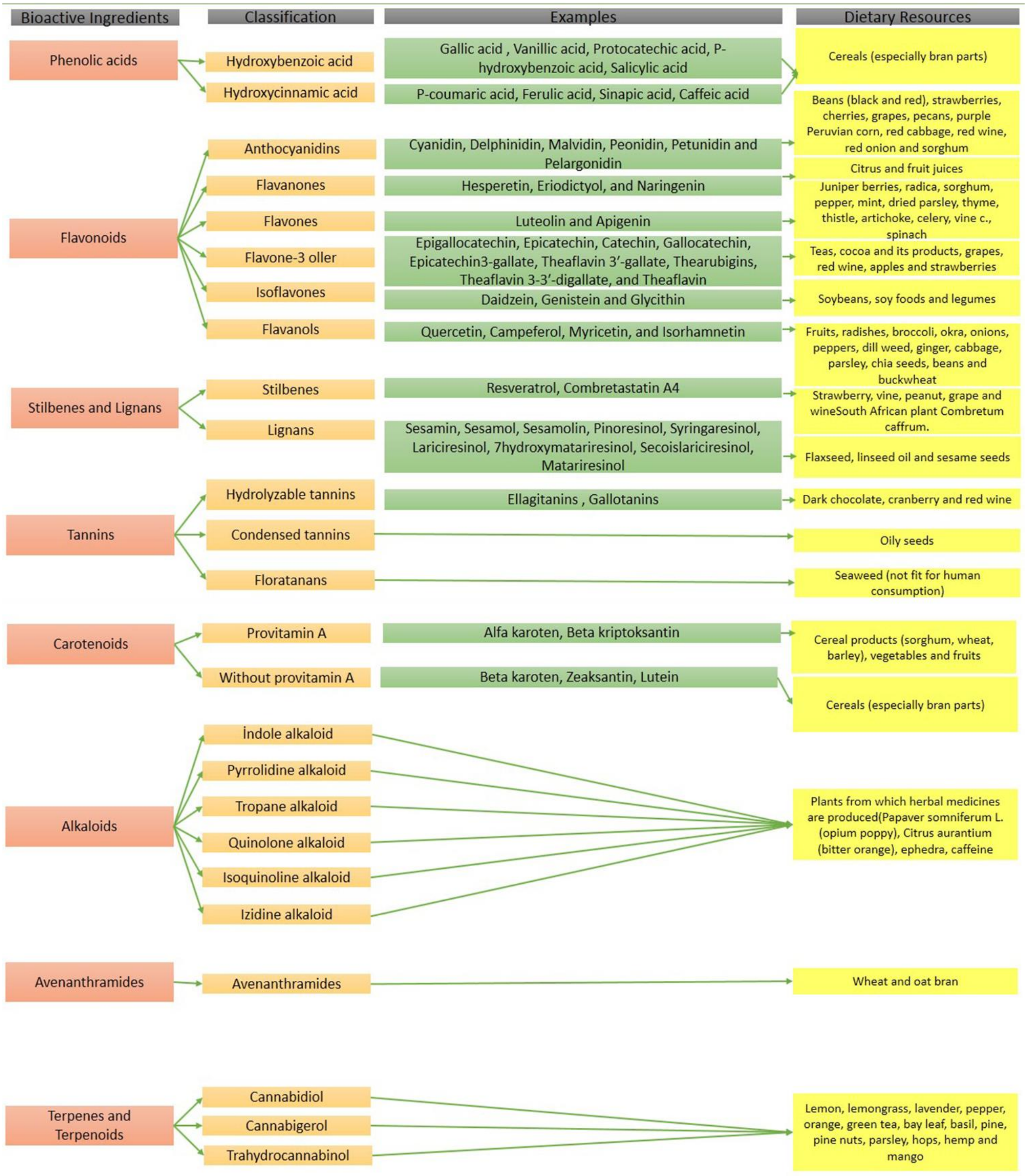

Figure 2. Bioactive components and their sources (Adapted from Banwo et al., 2020)

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Resveratrol can protect the ovarian tissue from the damage of reactive oxygen species (Liu et al., 2013). Quercetin modulates ovarian activity by regulating cell steroidogenic activity and correcting hormonal indices (Shah, Patel, 2016). Curcumin can boost the antioxidant defense system's capacity by upregulating antioxidant enzymes. It then acts as an antioxidant by removing harmful reactive oxygen species from the ovarian tissue (Wang, Zhang, Diao, Zhang, 2017). The most researched polyphenols in female reproduction are phytoestrogens, which include flavonoids and lignans. Because phytoestrogens have a similar structure to estradiol, they can bind to the estrogen receptor. There are two estrogen receptors, each of which has a different distribution and is encoded by different genes. The estrogen receptor is primarily found in the uterus and is responsible for endometrial proliferation; however, it is also found in ovarian granulosa cells, mammary glands, the hypothalamus, and the pituitary gland. Although 17-estradiol is more efficient for active estrogen receptors, phytoestrogens can be agonists or antagonists depending on the concentrations of phytoestrogen and 17-estradiol, competing with the hormone for binding sites (Sunita, Pattanayak, 2011).

The Mediterranean diet's high bioactive component content generally has a positive impact on reproductive health due to its antioxidant characteristics and ability to lessen hormonal and metabolic abnormalities. Application of a customized Mediterranean diet plan in accordance with the needs of the individual will be advantageous for appropriate and balanced consumption.

2.2. Dietary Fiber

Among other things, dietary fiber is classified based on its origin, solubility, gel formation/thickening/viscosity, and fermentability. Figure 3 summarizes the various types of dietary fibers and nutritional sources found in foods such as vegetables, fruits, grains, and legumes, which are cornerstones of the Mediterranean diet (Rezende, Lima, Naves, 2021).

Subfertility pathophysiology includes oxidative stress and insulin resistance. Whole grains and their constituents can improve fertility by providing anti-inflammatory, antioxidant, and glucose metabolism-friendly properties. Lignan, a phytoestrogen found in whole grains, may be beneficial for reproduction due to its proestrogenic and antiestrogenic properties (Adlercreutz, 2007). A high-fiber diet was linked to lower estradiol levels in a study of menstruating women. Low estrogen levels have been linked to increased fiber consumption, which reduces fecal-glucuronidase activity and lowers estrogen reabsorption (Zhang, Mumford, Gaskins, 2009). There was no correlation between added sugar consumption (72 g/day versus 27 g/day) or high/ low fiber intake (16 g/day versus 25 g/day) with fertility in a North American cohort (Fontana, Della Torre, 2016).

One of the best methods for controlling gut flora is dietary fiber. The gut microbiota's ability to use pulp is influenced by several variables, including its fermentability, solubility, and viscosity, all of which influence the phylum, family, and species level changes in pulp and microbiota. The microbiota can digest dietary fiber and creates a variety of metabolites, including short-chain fatty acids

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(butyrate, acetate, and propionate). Diets low in fiber may cause a reduction in the synthesis of these fatty acids (y Abreu et al. 2021).

It is well known that dietary fiber has an indirect effect on hormones via the microbiome. One of the primary regulators of circulating estrogens is the gut microbiome. The estrobolome is the gene repertoire of the gut microbiota that may metabolize estrogens (Plottel, Blaser, 2011). Estrogen affects the female reproductive system by indirectly increasing lactobacillus abundance and lactic acid production, decreasing vaginal pH, increasing glycogen levels, increasing mucus secretion, and strengthening the vaginal epithelium (Baker, Nakkash, Herbst-Kralovetz, 2017). Microbially produced β-glucuronidase converts conjugated (inactive) estrogens to deconjugated (active) estrogens. These deconjugated and unbound "active" estrogens are absorbed into the bloodstream and act on estrogen receptors (Plottel, Blaser, 2011). Estrogens can have a genomic impact by attaching to estrogen receptors, causing downstream gene activation and epigenetic consequences, and initiating intracellular signaling cascades. This link leads to physiological changes in tissues ranging from reproductive health to neural development.

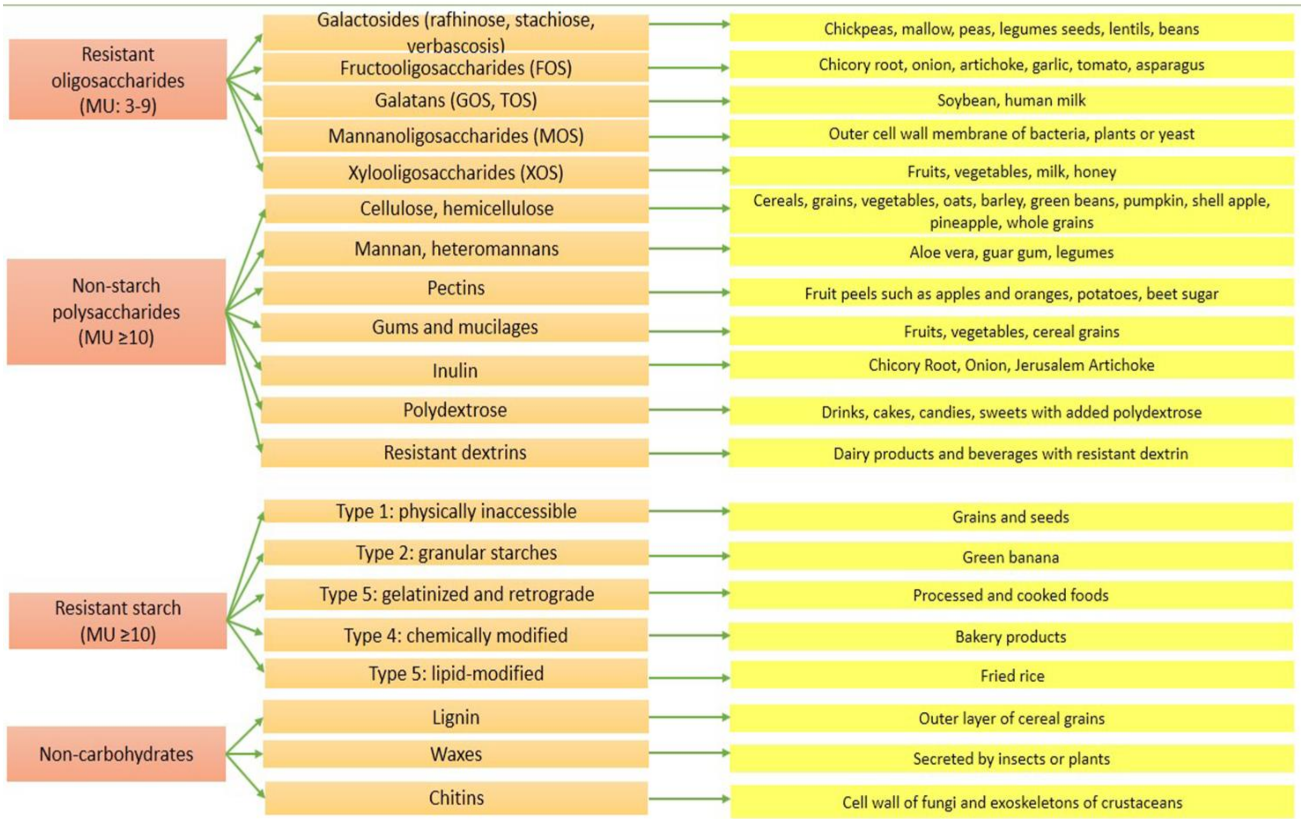

Figure 3. Dietary fiber classifications and dietary sources (Adapted from Rezende, et al., 2021)

A decrease in circulating estrogen is caused by a lack of bacteria that break down estrogen, which may have an impact on hypoestrogenic-related disorders (Baker et al., 2017). The Mediterranean diet's adequate fiber content appears to influence reproductive health through microbiota, metabolism, and hormonal regulation.

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2.3. Polyunsaturated Fatty Acids

The Mediterranean diet is a balanced diet of essential polyunsaturated fatty acids such as linoleic acid (LA, ω-6) and alpha-linolenic acid (ALA, ω-3) found in plant foods, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in oily fish (Lăcătușu et al., 2019).

Polyunsaturated fatty acids can play a variety of roles in the biology and metabolism of the oocyte. Unsaturated free fatty acids with two or more double bonds are classified as omega-3 and omega-6. The ω -3 and ω -6 fatty acids are obtained through diet, and the amount consumed affects the availability of these fatty acids (Weber, Fischer, Schacky, Lorenz, Strasser, 1986). They are essential fatty acids because humans cannot produce omega-3 fatty acids such as EPA and DHA. They are especially important for embryo-fetal development because they play a vital role in neuronal membranes. DHA, in particular, is the primary component of phospholipids, which play a role in membrane signaling, membrane flexibility, and ion channel and receptor function (Arnoldussen, Kiliaan, 2014).

IVF cycles, which are one of the most commonly used treatments for infertility, are extremely ineffective because the oocytes' ability to develop into viable embryos is significantly lower than it would be in a healthy environment. Oocyte quality is a key determinant of female fertility, affecting not only fertilization but also embryo growth, implantation, and pregnancy (Rienzi, Vajta, Ubaldi, 2011). Oocyte quality is directly affected by diet and maternal metabolic state. During the IVF process, the concentration of lipids and fatty acids in the follicular microenvironment or the oocyte culture medium is correlated with quality and development (Fayezi, Leroy, Novin, Darabi, 2018). Although the composition of cellular proteins is genetically determined, the structure of the cell membrane is affected by dietary polyunsaturated fatty acids. Since they are a crucial part of membranes and play a role in embryo growth and implantation as well as in a variety of other activities, including fluidity and flexibility, polyunsaturated fatty acids are thought to have a significant role in infertility (Simopoulos, 2008).

Elongation and desaturases, two metabolic enzymes, are known to be shared by ω-6 and ω-3 oil acids. A functional decrease in one of these families may increase the other. In this context the ratio ω-6: ω-3 is commonly used to describe the relationship between these fatty acids. These two fatty acid classes are incompatible, i.e., they have distinct metabolic and physiological properties (Simopoulos, 2008). It is critical to maintaining an optimal ratio of ω-6 and ω-3 fatty acid intakes in order to maintain reproductive health. The majority of polyunsaturated fatty acids in the modern western diet are omega-6 fatty acids, with a ω-6: ω-3 fatty acid ratio ranging from 10:1 to 25:1, far from the recommended diet fatty acid pattern. When a diet is supplemented with ω-3 fatty acids, ω-6 fatty acids are largely replaced in almost all cell membranes, as in the Mediterranean dietary model (Simopoulos, 2002). A Mediterranean diet with a 4:1 fatty acid ratio of ω-6 to ω-3 has been shown to promote the incorporation of ω-3 fatty acids into cell membranes (Jungheim, Frolova, Jiang, Riley, 2013).

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A lower ratio of ω -6:ω -3 fatty acids in the follicular fluid has been linked to a lower likelihood of conceiving using assisted reproductive technology. According to research on the fatty acid composition of human follicular fluid, higher oleic, palmitic, linoleic, and stearic acid levels were linked to a lower percentage of oocyte complexes with a desirable shape (Hammiche, 2011). Women who did not get pregnant after IVF treatment had higher levels of palmitic, linoleic, and stearic acids in their follicular fluid (Jungheim, 2011).

Significant connections between dietary consumption of ω-3 fatty acids (ALA and DHA) and post-IVF embryo morphology were found in a study (n=235) in which women's dietary intake of ω-3 fatty acids were followed for 4 weeks before IVF (Mirabi et al., 2017).

In the EARTH study, high serum ω-3 fatty acid concentrations were linked to an increased likelihood of clinical pregnancy and live birth (Chiu et al., 2018). In one study, blood and follicular liquid fatty acids were measured in 105 women undergoing IVF. After controlling for age and BMI, they discovered that total fatty acids corresponded to high-quality oocytes and that EPA levels in pregnant women were significantly higher than in non-pregnant women (Jungheim et al., 2011). In another study (n=100) of women undergoing IVF therapy, researchers discovered that ω-3 fatty acid concentrations were linked to a higher likelihood of clinical pregnancy and live birth, and they claimed that the relationship was due to EPA. Additionally, the likelihood of clinical pregnancy and live birth increased by 8% for every 1% rise in serum ω-3 fatty acid levels. Although the relationship between serum linoleic acid and ω-6:ω-3 was inversely associated with data such as peak estradiol concentration and oocyte yield, clinical outcomes did not seem to be affected (Chiu et al., 2018). Consuming ω-3 fatty acids and the efficacy of IVF have often yielded uneven and conflicting outcomes in studies involving small groups. There is a lack of studies regarding the results of eating a diet high in ω-3 fatty acids before IVF.

The follicles contain a small amount of ω-3 fatty acids, which are physiologically more prevalent in the granulosa cells than in the oocyte. ω-3 fatty acids can influence oocyte maturation and development by altering the metabolism and function of granulosa cells, particularly by controlling peroxisome proliferator-activated receptors (PPAR). Activation of PPAR-γ has a positive effect by reducing the production of estradiol, progesterone, and β-oxidation-induced ATP in cumulus-granulosa cells, which have a negative effect on embryo viability and development.ω-3 fatty acids, on the other hand, are thought to control cyclooxygenase-2 gene expression and activity, resulting in ovulation, oocyte maturation, and embryo development by substituting 2 series prostaglandins with 3 series analogs. The incorporation of omega-3 fatty acids into the plasma membrane may promote peroxidation by causing lipid instability. ω-3 fatty acids can have both positive and negative effects on oocyte maturation and embryo development by altering metabolic processes and the membrane characteristics of cyclooxygenases (Zarezadeh, et al, 2019).

These findings imply that dietary or metabolic modifications to polyunsaturated fatty acids may

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increase the likelihood of successful IVF implantation, but more research is required.

2.4. Monounsaturated Fatty Acids

The Mediterranean diet also encourages the consumption of oleic acid (w-9), one of the monounsaturated fatty acids present in olive oil, in addition to polyunsaturated fatty acids (Lăcătușu et al., 2019).

It has been demonstrated that oleic acid, a monounsaturated fatty acid, can support healthy oocyte and embryo development, which is relevant to the impact of oleic acid on the outcomes of IVF (Mirabi et al., 2017; Jahangirifar, Taebi, Nasr-Esfahani, Heidari-Beni, Asgari, 2021).

Monounsaturated fatty acids (MUFA) reduce inflammation and promote fertility through binding to the PPAR-gamma receptor. According to studies, MUFA consumption and plasma levels are positively correlated with fertility and gestational age (Mumford et al., 2018; Comerford, Ayoob, Murray, Atkinson, 2016)

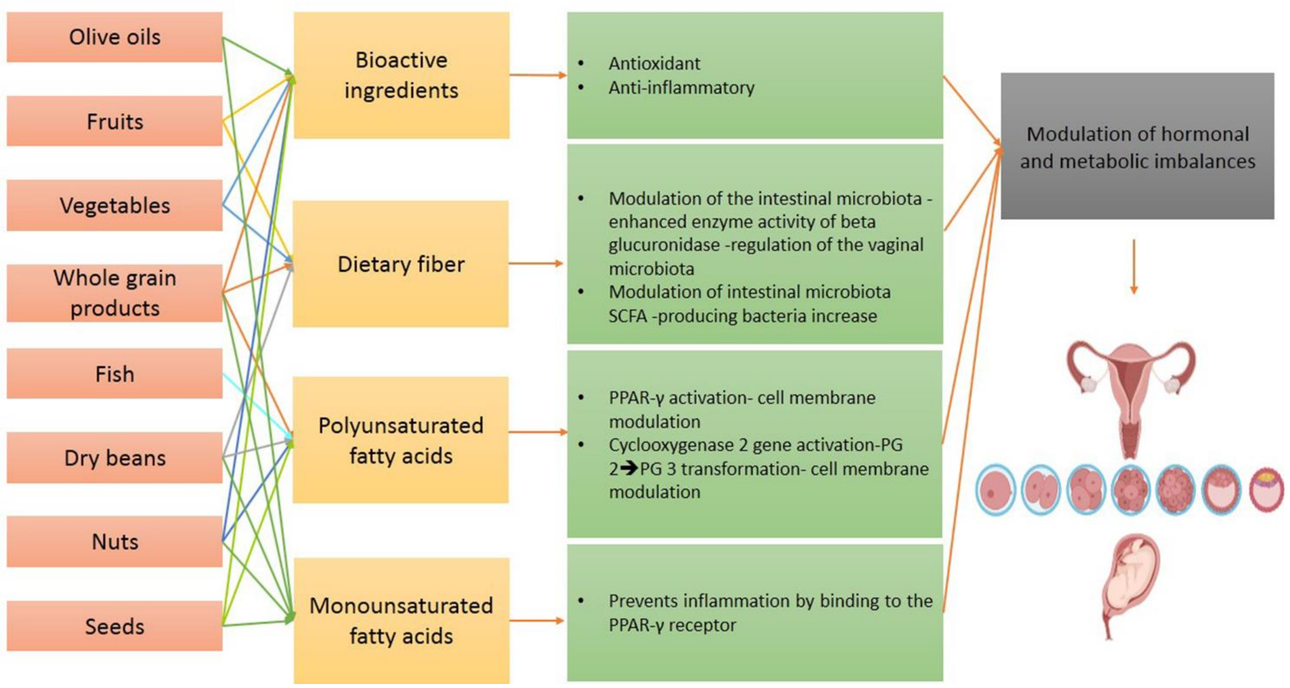

Figure 4. Mediterranean Diet Components and Possible Effects on Female Reproductive Health (BioRender was used for images)

Polyunsaturated and monounsaturated fatty acids appear to have beneficial effects on female infertility in general when an appropriate and balanced diet is offered. Now, rather than quantity, the quality of the oil takes the center stage. According to this knowledge, it would be advantageous to include fatty fish, canola oil, flaxseed oil, olive oil, avocado, and almonds in the diet of women who are ready to get pregnant.

Figure 4 summarizes the potential biochemical pathways of the effects of the Mediterranean diet's components on female reproductive health.

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3. Conclusion

The Mediterranean diet has been shown to improve reproductive health by including plant-based foods. To achieve the desired results, antioxidant, anti-inflammatory, microbiota, and cell membrane modulation are expected to positively alter hormonal and metabolic imbalances.

Although the Mediterranean diet has been shown to improve the outcomes of assisted reproductive therapy, incorporating this type of nutrition into routine clinical practice to improve health conditions does not appear to be an easy task. The Mediterranean diet is described in the literature in terms of daily or weekly consumption. There are no recommendations based on specific requirements. Because only portion recommendations are given and portions differ from country to country, it is unclear how the Mediterranean diet will be implemented on an individual basis. As a result, the individual's nutritional status is not fully met according to their needs, which is the most important point for adequate and balanced nutrition. To properly provide an individual with a sufficient and balanced diet, the Mediterranean diet pattern should be expanded in terms of applicability. To better understand how the Mediterranean diet and female infertility are related, it appears necessary to customize the diet and assess its effects on metabolism using randomized controlled trials. Women of childbearing age require counseling and recommendations that are tailored to their specific needs to improve their nutritional status and raise healthy children.

Conflicts of interest

There are no conflicts of interest to declare.

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