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REVIEW

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A disturbed communication between hypothalamic-pituitary-ovary axis and gut microbiota in female infertility: is diet to blame?

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Abstract

Female infertility is a multifactorial condition influenced by various genetic, environmental, and lifestyle factors. Recent research has investigated the significant impact of gut microbiome dysbiosis on systemic inflammation, metabolic dysfunction, and hormonal imbalances, which can potentially impair fertility. The gut-brain axis, a bidirectional communication system between the gut and the brain, also plays a significant role in regulating reproductive functions. Emerging evidence suggests that the gut microbiome can influence brain functions and behavior, further emphasizing the importance of the microbiota-gut-brain axis in reproduction. Given their role as a major modulator of the gut microbiome, diet and dietary factors, including dietary patterns and nutrient intake, have been implicated in the development and management of female infertility. Hence, this review aims to highlight the impact of dietary patterns, such as the Western diet (WD) and Mediterranean diet (MD), and to decipher their modulatory action on the microbiota-gut-brain axis in infertile women. By contrasting the detrimental effects of WD with the therapeutic potential of MD, we emphasize the pivotal role of a balanced diet rich in nutrients in promoting a healthy gut microbiome. These insights underscore the potential of targeted dietary interventions and lifestyle modifications as promising strategies to enhance reproductive outcomes in subfertile women.

Keywords Western Diet, Mediterranean Diet, Microbiota, Female infertility, Hypothalamic-pituitary Axis, Gut-Brain Axis

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Narrative Review.

Background

According to the World Health Organization (WHO) and the American Society of Reproductive Medicine (ASRM), infertility is defined as the inability to conceive a child after one or more years of regular, unprotected sexual intercourse [1, 2]. Infertility is a major health burden to patients and healthcare systems, affecting 15% of couples of reproductive age worldwide [3] and approximately 50% of all women in developing countries [4].

The hypothalamic-pituitary-ovarian (HPO) axis is a tightly regulated system that controls female reproduction, including ovulation and pregnancy. In a normally functioning HPO axis, the hypothalamus releases gonadotropin-releasing hormone (GnRH), which signals the pituitary gland to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH stimulate the ovaries to produce estrogen and progesterone, which are essential for ovulation and pregnancy [5].

Over the past decade, it has become evident that signaling communication between the gut microbiota and the brain occurs through neural pathways, which also contribute to the regulation of the HPO axis [6]. This communication is part of what is known as the microbiota-gut-brain (MGB) axis, a bidirectional pathway between gut bacteria and the central nervous system (CNS). This axis profoundly influences and regulates a range of body functions including the reproductive function [7, 8]. Recently, significant attention has been directed towards understanding the bidirectional crosstalk between the gut and the brain [9].

Diet has recently been shown to play a significant role in shaping the composition of the gut microbiota. Certain dietary patterns may promote a diverse and beneficial gut microbiome, which could positively impact reproductive health. Conversely, an imbalanced or unhealthy diet might lead to dysbiosis, an unfavorable alteration in the gut microbiota, potentially affecting hormonal regulation, inflammation, and other factors relevant to fertility [10]. Given the substantial evidence related to the role of diet in determining the composition and profile of the gut microbiome, researchers have suggested that diet could be a potential target to maintain a healthy MGB axis and, hence a functional HPO axis [8, 11, 12]. Adjustments in diet, such as selenium supplementation [13], could help restore balance in the gut microbiota, potentially improving hormonal regulation and reducing inflammation, thereby enhancing reproductive outcomes. This could be particularly relevant for infertile women, as their reproductive systems might already be under specific challenges [14].

Considering the intertwined communication between the HPO and MGB axes and the importance of balanced hormonal levels regulated by the HPO axis in maintaining women's fertility, along with the emerging role of diet in promoting a healthy microbiota, this literature review aims to explore the female fertility-related alterations in the gut microbiome and the effect on HPO axis induced by contrasting dietary patterns, such as the Western Diet (WD) and the Mediterranean diet (MD). Additionally, the review will highlight the role of microbial metabolites and gut-brain peptides or hormones in the bidirectional communication between the gut and the brain, focusing on their impact on modulating complex behaviors and fertility.

Search methods

Studies related to the topic were identified and selected by using the following searching engines: MEDLINE, PubMed, and Google Scholar databases, and references from peer-reviewed original research articles, meta-analyses, systematic reviews, and narrative reviews using the following search terms: "Western diet"; "Mediterranean diet"; "female infertility"; "gut-brain axis"; "gut microbiome"; "microbiota-gut-brain axis"; "mental health"; "obesity"; "hypothalamic-pituitary-ovarian axis"; "vitamins"; "probiotics"; and "gut-brain mediators". Searches were conducted between August 2023 and June 2024. All articles published in English language and between 1973 and 2024 were included. Studies not directly relevant to the interaction between diet, gut microbiota, and female infertility as well as animal studies that did not provide translational relevance to human health were excluded.

Etiology of female infertility and related therapeutic approaches

Female infertility can be attributed to a variety of factors, including ovulatory dysfunction, PCOS, fallopian tube blockage, age-related fertility decline, endometriosis, and other pelvic inflammatory conditions [15–17]. Hormonal imbalance stemming from endocrine system disorders may include hypothyroidism (insufficient production of thyroid hormone by the thyroid gland disrupting ovulation) [18], premature ovarian insufficiency (the cessation of ovarian function prior to the age of 40) [19], hyperprolactinemia (excess production of prolactin by the pituitary gland interfering with ovulation) [20], hypopituitarism (the deficiency in LH and/or FSH secreted by pituitary gland interfering with follicle development) [21], and congenital adrenal hyperplasia (CAH) (a genetic disorder in which the adrenal glands produce too much androgens disrupting normal menstruation) [22].

It is estimated that 50% of women suffering from infertility are likely to respond successfully to treatment [15]. After identifying the underlying cause of female infertility and considering factors such as the woman's age, history of previous pregnancies, and the duration of infertility,

physicians select the most appropriate treatment options [16]. In many cases, infertility resulting from ovulation disorders is highly treatable and can be effectively managed with medications, such as oral ovulation-inducing agents, within a primary clinical setting [16]. The oral administration of Clomiphene Citrate or Letrozole may be required to stimulate the release of FSH and LH [23] and drive ovulation. Human Chorionic Gonadotropin (hCG), the placental homolog of LH, which is known as "the hormone of pregnancy," may also be prescribed to trigger the release of the egg following follicular development [24]. For pelvic conditions such as endometriosis or tubal disease, surgical intervention or assisted reproductive technology (ART) may be recommended [25].

Although ART interventions, such as in vitro fertilization (IVF), have proven to be highly effective, resulting in the birth of over 5 million children in the past three decades, their availability remains limited, unevenly accessible, and often unaffordable for many in low- and middle-income countries [26–28]. Furthermore, research has increasingly emphasized the importance of a healthy and balanced diet in enhancing the success rates of ART procedures and improving female fertility overall. Notably, numerous studies suggest that a healthy gut microbiota, fostered by a nutritious diet, plays a vital role in various aspects of reproductive health, including fertility. The composition and diversity of gut bacteria can influence hormone regulation, immune function, and inflammation, all of which are critical factors affecting fertility [29, 30]. In general, the dominance of certain gut microbial species, mainly *Lactobacillus*, *Acinetobacter*, *Pseudomonas*, *Fusobacterium*, *Bacteroidetes*, and *Preovotella* species has been linked to proper reproductive health and functions. However, the presence of pathogenic bacteria such as *Ureaplasma*, *Escherichia coli*, *Enterococci*, *Enterobacteriaceae*, *Streptococci*, and *Staphylococci* is thought to be associated with reproductive dysfunctions [31]. It has been shown that alterations in the gut microbiome composition and abundance, leading to gut microbiome dysbiosis, are associated with various types of female infertility, including polycystic ovary syndrome (PCOS) [32]. Specifically, a significant abundance of *Parabacteroides* and *Clostridium* has been reported in PCOS patients, in contrast to the enrichment of *Faecalibacterium*, *Bifidobacterium*, and *Blautia* in their control counterparts [32].

Nature vs. nurture-based risk factors involved in the pathophysiological mechanisms of infertility

Female infertility is associated with various risk factors, which can be broadly classified into two categories: nature (genetic and physiological) and nurture (lifestyle and environmental) factors.

Lately, there has been a growing interest in investigating the impact of lifestyle factors on infertility. Lifestyle factors refer to modifiable habits that can significantly affect a person's overall health and fertility. Several lifestyle factors have been identified and studied, including (i) the cluster of smoking, drug abuse, and alcohol consumption, adversely affecting egg quality and fertilization [33–35], (ii) lack of physical activity, promoting obesity and hormonal disruption [36], (iii) stress and anxiety, suppressing hormone production (FSH and LH) [37–39], (iv) sleep problems, disrupting the circadian rhythm leading to infertility [40] and (v) poor nutrition, interfering with the HPO axis and hindering oocyte function [41].

These mechanisms play a critical role in inflammatory processes, with oxidative stress, mitochondrial dysfunction, hypoxia, inflammation, and hormonal imbalances—particularly those caused by dysregulation of the HPA axis—being the most prominent pathophysiological factors linked to female infertility. For example, studies in mice have demonstrated that a deficiency in SIRT1, a protein that enhances antioxidant defences, can lead to reduced ovarian reserve and subsequent infertility. This occurs through the mediation of increased Reactive Oxygen Species (ROS), mitochondrial dysfunction, and DNA damage in oocytes [42–44]. Another study investigated the effects of chronic hypoxia exposure during fetal development in female rats and found that it led to a decreased ovarian reserve and accelerated ovarian aging. These changes negatively impacted the fertility of the offspring in the next generation, suggesting that prenatal environmental factors can have lasting consequences on reproductive health [45]. In humans, inflammation can have detrimental effects on fertility, including disruption of menstrual cycles, implantation failure, and recurrent miscarriages, however, it is possible to mitigate the inflammatory environment in the female reproductive system through appropriate nutritional strategies and other non-pharmacological approaches [46].

Infertility is widely recognized as a multidimensional stressor linked to mental health disorders. Both infertility and its treatments can lead to increased stress, depression, and anxiety, with the severity of anxiety positively correlated with the duration of infertility [47]. Moreover, depression was shown to be more prevalent and positively correlated with treatment failure [48]. Mental health is a component of the gut-brain axis. A group of 1146 patients experiencing infertility underwent assessments using the Generalized Anxiety Disorder 7 (GAD-7) [49], or "excessive and persistent worrying that is hard to control, causes significant distress or impairment, and occurs on more days than not for at least six months" [50] alongside a simple and multiple logistic method of classification. The results indicated that generalized anxiety is prevalent among women experiencing infertility,

with a positive correlation observed between higher levels of anxiety, lower educational attainment, and longer duration of infertility. Moreover, based on the analysis of Patient Health Questionnaire-9 (PHQ-9) scores, depression was shown to be prevalent in infertile women (30.5% of 1506 infertile patients) and was positively correlated with treatment failure [51]. Ovarian hormones have been linked to depression and anxiety risk in females through their influence on brain morphology, neurochemistry, and function [52]. Specifically, estrogen and progesterone have a significant neuromodulatory role, as shown by both preclinical and clinical studies, thus affecting female emotionality [53, 54]. Estrogen receptor β (Erβ) has been linked to depression in various studies, suggesting a role for estrogen as an anxiolytic and antidepressant in women [55]. Moreover, numerous studies have investigated the anxiolytic properties of progesterone through positive allosteric modulation of the γ-aminobutyric acid (GABA) receptor complex [56–58].

The impact of the Western Diet on MGB axis in infertile women

WD is characterized by a high intake of processed foods, red and processed meats, sugary and fatty foods, and low consumption of fruits, vegetables, and whole grains [59]. WD has been shown to negatively affect the composition and diversity of the gut microbiota [60]. However, the clear mechanism is not yet understood. There are many potential pathways through which WD can exacerbate the pathophysiology of infertility by disrupting the MGB and, specifically, the HPO axis (Table 1).

These effects are likely dose-dependent, as the greater consumption of processed foods, saturated fats, and refined sugars exacerbate the detrimental outcomes of WD, since it can lead to obesity, which has been associated with disruptions in the HPO axis, resulting in decreased ovarian reserve [61, 62], anovulation, abnormal uterine bleeding, endometrial hyperplasia [63, 64] mitochondrial dysfunction [62] and irregular menstrual cycle [65]. Studies indicate that obese women tend to have lower LH levels, potentially leading to dysfunctional ovarian folliculogenesis, manifested in longer follicular phases [66]. Moreover, excess body fat can disrupt the delicate balance of hormones involved in ovulation, including decreased LH levels, decreased ovarian steroid hormones progesterone (P4) levels, and increased estradiol (E2) levels, ultimately leading to reduced fertility [67]. The accumulation of adipose tissue in case of severe hyperandrogenism and hyperleptinemia has been associated with ovarian dysfunction, encompassing altered follicular fluid composition and granulosa cell signaling. Additionally, a high adipokine profile following HFD consumption interferes with GnRH secretion and consequently alters the levels of pituitary hormones LH and FSH and ovarian hormones E2 and P4. An expected increase in insulin levels due to WD consumption influences fertility by elevating GnRH and LH levels [68] (Fig. 1). Several confounding factors, such as physical activity, may influence these observed effects since they can mitigate some of WD's pro-inflammatory effects and improve metabolic health, potentially attenuating its impact on fertility [69].

Due to its pro-inflammatory nature, WD has been associated with chronic low-grade inflammation and increased gut permeability (leaky gut), which can also contribute to conditions such as endometriosis and pelvic inflammatory disease [70]. A study conducted by Patel et al. (2018) found that women with a history of infertility had a different gut microbiota composition compared to fertile women [71]. It was characterized by the enrichment of *Hungatella*, which is associated with the production of the proatherogenic compound trimethylamine N-oxide (TMAO), a fundamental factor that drives inflammation. In several studies, WD was linked to lower levels of beneficial bacteria such as *Eubacterium* species and *Bifidobacterium* [72, 73]. These bacteria are classified as short-chain fatty acids (SCFAs) producers with anti-inflammatory properties. Additionally, the abundance of *Bifidobacterium* was suggested to be an indicative biomarker of a successful pregnancy following ART [74] (Fig. 1).

The low dietary fiber content is another factor contributing to the detrimental effects of this unhealthy diet. The fermentation of fibers by specific microbes in the gut is responsible for the production of SCFA, such as butyric acid, acetate, and propionate [75]. Reduced SCFA production may contribute to gut microbiome dysbiosis, oxidative stress, and inflammation, which can potentially induce infertility or exacerbate its pathophysiology and outcomes [29, 76, 77]. Furthermore, fiber intake, which influences microbiota-derived metabolites, especially SCFAs, may lead to alterations in estrogen and progesterone levels in the female body [78]. An animal study by Lu, Naisheng et al. [79] showed the effect of SCFAs on E2 and P4 production. The treatment of porcine granulosa cells (PGCs) with butyric acid (BA) can regulate the synthesis of P4 and E2 via the cyclic adenosine monophosphate (cAMP) signaling pathway in a dose-dependent manner. Lower concentrations of BA (0.05 mM) were found to greatly stimulate P4 secretion and slightly stimulate E2 secretion in PGCs, while higher concentrations of BA (5 mM) significantly inhibited P4 secretion and increased E2 levels [79]. Basically, the gut microbiota primarily controls estrogen levels through the secretion of the gut microbial β-glucuronidase (gmGUS) enzyme by *Lactobacillus*, *Clostridium*, *Bacteroides fragilis* and other *Bacteroides* species, *Ruminococcus gnavus* [80]. This enzyme can convert conjugated estrogen

Table 1 A summary of the effects of WD, MD and probiotic supplementation on MGB axis and female infertility

Dietary patterns/ supplementation	Associated physiological and molecular mechanism	Impact on MGB axis	Impact on fertility	Ref
Western Diet	• ↑ risk of metabolic disorders • obesity and excess body fat • chronic low-grade inflammation • ↑ gut permeability • mitochondrial dysfunction • oxidative stress • ↑ gut microbial β-glucuronidase (gmGUS) activity • ↓ CCK activity	• HPO disruptions: - ↑ E2 levels - ↓ LH levels - ↓ P4 levels - ↑ GnRH levels • cognitive dysfunctions (including memory deterioration), emotional disorders, depression • anxiety-like behavior • gut microbiome dysbiosis: - ↑ *Firmicutes/Bacteroidetes* ratio (↑ *Lactobacillus spp.*, *Bacteroides spp.*, and *Enterococcus spp;* ↓ *Enterobacter* spp. and *Clostridium leptum)* - ↓ levels of beneficial bacteria such as *Eubacterium* species and *Bifidobacterium* - ↑ class *Bacteroidia* (species *Bacteroides* and *Parabacteroides*) and class *Clostridia* (species *Oscillospira* and *Coprococcus* • ↓ SCFA production • ↑ TMAO production • ↑ LPS production	• irregular menstrual cycle • ↓ ovarian reserve • perturbed ovarian folliculi-genesis and ovulation • anovulation • endometrial hyperplasia • endometriosis • abnormal uterine bleeding • altered follicular fluid composition and granulosa cell signaling • alterations in estrogen and progesterone levels • ↓ ART success rate	[57, 72, 74, 77–83, 87, 88, 90, 93, 95, 98–102, 104, 108–110]
Mediterranean Diet	• anti-inflammatory and neuro-modulator role • antioxidant role • healthy gut lining • improved metabolic health (favorable changes in insulin resistance, reduced risk of obesity) • activation of GLP-1 pathway • vitamins D and E action on the antioxidant pathways • PUFA anti-inflammatory activity	• ↓ LH and FSH levels • ↑ estrogen and progesterone levels • ↑ microbial diversity • ↑ abundance of beneficial bacteria: *Akkermansia muciniphila*, *Prevotella*, *Lactobacillus*, *Enterococcus* and *Bifidobacterium* • ↓ abundance of *Clostridium* • ↑ levels of fecal SCFA • Potential treatment approach for neuropsychological disorders with neuroprotective effects • ↓ risk of depression, anxiety, and stress • Improved mental and physical health	• improved pregnancy rate (100%) • improved egg quality • improved ovarian functions • ↑ success rates of ART procedures • ↓ risk of developing PCOS • rescuing the ovulatory dysfunction phenotype in the PCOS mouse model	57, 72, 74, 77–83, 87, 88, 90, 93, 95, 98–102, 104, 108–110]

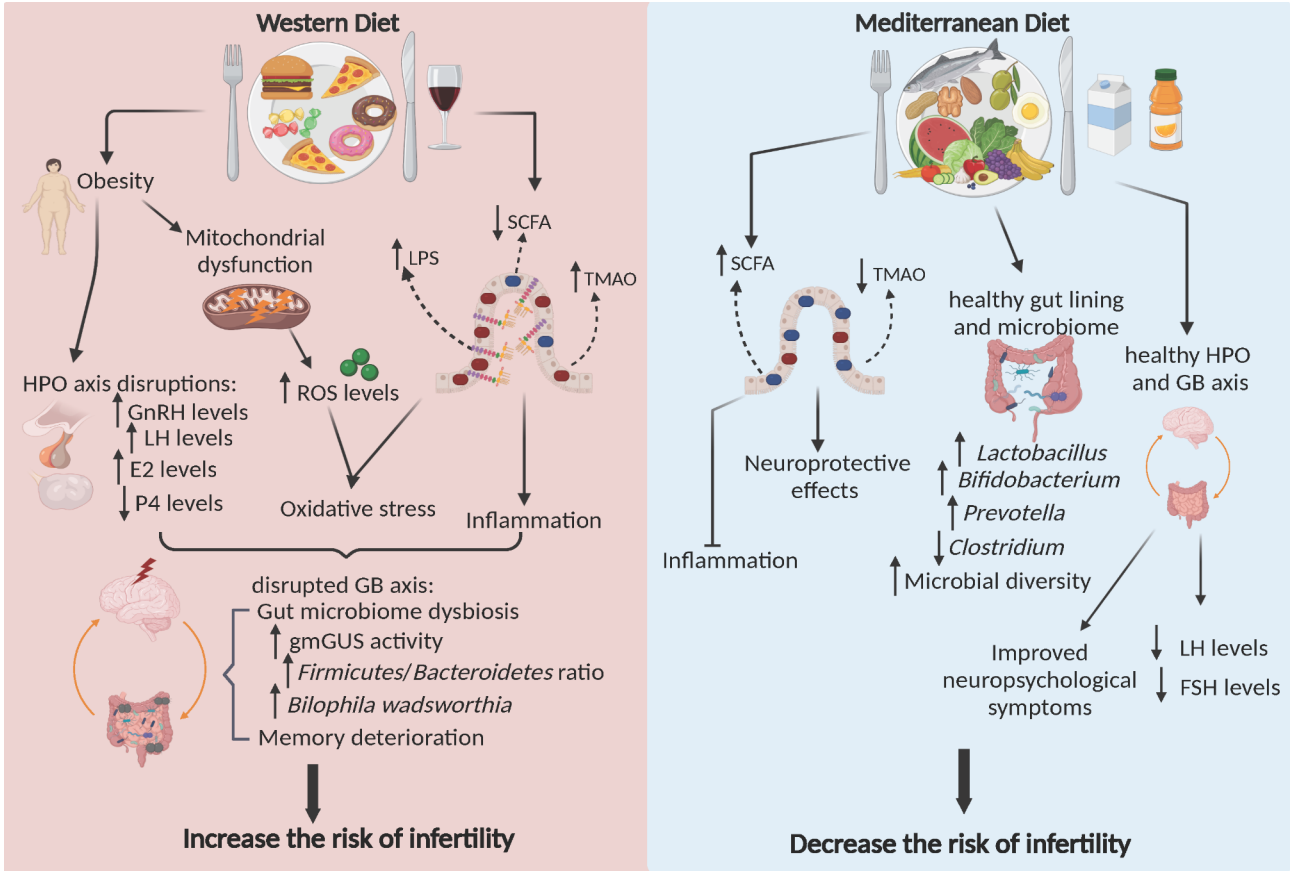

Fig. 1 Error! Reference source not found. Suggested mechanisms by which Western diet (WD) and Mediterranean diet (MD) can alter the risk of female infertility. HPO: Hypothalamic-pituitary-ovarian; GnRH: gonadotropin-releasing hormone; LH: gonadotropin-releasing hormone; FSH: follicle-stimulating hormone; E2: estradiol; P4: progesterone; GB: gut-brain; ROS: reactive oxygen species; gmGUS: β-glucuronidase; LPS: lipopolysaccharide; SCFA: short-chain fatty acids; TMAO: trimethylamine N-oxide

into deconjugated estrogen in the gastrointestinal (GI) tract, which can then bind to estrogen receptors, triggering subsequent signaling [80]. High fat and low fiber diets, which are the main characteristics of the WD, are associated with higher gmGUS activity compared to vegetarian or high soluble fiber diets [81, 82]. An increase in gmGUS activity is associated with gut microbial dysbiosis and elevated estrogen levels, which have been linked to endometriosis [78]. Additionally, endometriosis patients showed higher levels of two bacteria that belong to class *Bacteroidia* (*Bacteroides* and *Parabacteroides*) and two others that belong to class *Clostridia* (*Oscillospira* and *Coprococcus*) [83].

Unlike the lower levels of SCFA, TMAO is shown to be present in high levels in case of female infertility [71] or unsuccessful IVF attempts, where it can induce inflammation and oxidative stress pathways [84]. TMAO is a secondary metabolite formed by hepatocytes via the oxidation of trimethylamine (TMA). TMA is absorbed from the intestine following the catabolism of nutrients derived from red meat, such as dietary choline and L-carnitine, which are highly abundant in WD [85]. Dysregulation of the microbiota–gut–brain axis has even been actively investigated in the context of various psychiatric disorders. Interestingly, a study by Ohland et al. demonstrated that a very high-fat WD supplemented for a period of 21 days can disrupt the gut-brain axis in mice, leading to anxiety-like behavior [86]. This disruption was associated with changes in the gut microbiota, particularly an increase in *Firmicutes*/*Bacteroidetes* ratio and the abundance of *Proteobacteria* and *Spirochaetes*. The possible mechanisms underlying this alteration in the microbiome composition are attributed to a decrease in the total levels of SCFAs in cecal contents, including a reduction in the levels of acetic, propionic and butyric acids and an increase in the levels of caproic acid [86]. Moreover, mice supplemented with the western-like diet for 13 weeks showed an increase in Firmicutes (mainly *Ruminococcaceae* and *Lachnospiraceae*) and a decrease in Bacteroidetes in their gut microbiome, accompanied by a decrease in burrowing behavior and deterioration in memory evaluated by Morris water maze test [87]. Obesity is known to be associated with an increase in the ratio of Firmicutes to Bacteroidetes, the upregulation of

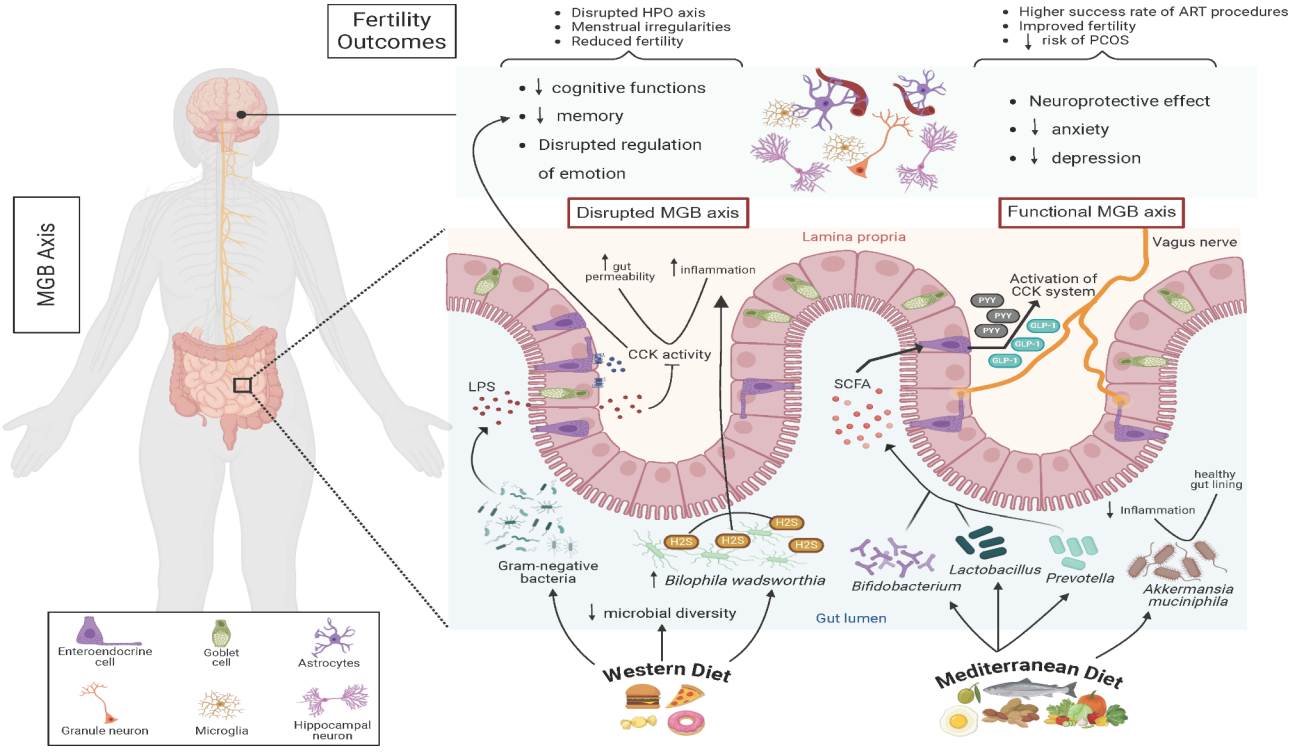

Fig. 2 Error! Reference source not found. The impact of gut-brain meditators (CCK, PYY, and GLP1) on MGB axis and female infertility. CCK: Cholecystokinin; PYY: peptide YY; GLP-1: glucagon-like peptide 1; H2S: hydrogen sulfide; MGB: microbiota-gut-brain; HPO: hypothalamic-pituitary-ovarian; PCOS: polycystic ovarian syndrome; SCFA: short-chain fatty acid; LPS: lipopolysaccharide

Lactobacillus spp., *Bacteroides* spp., and *Enterococcus* spp., and the downregulation of *Enterobacter* spp. and *Clostridium leptum* [88, 89]. Several animal and human studies have shown that obesity induced by a high-fat diet (HFD), such as WD, can lead to perturbations in the HPO axis, which are associated with anxiety and depression. This disruption also results in ovulation disturbances and decreased fertility [90, 91].

Additionally, a WD can enhance the production of lipopolysaccharide (LPS), a pro-inflammatory bacterial byproduct produced by all Gram-negative bacteria [92]. An increase in LPS induces inflammation and decreases Cholecystokinin (CCK) activity [93]. The CCK system consists of two receptors: the CCK1 receptor (CCK1R), which is predominantly expressed in the gastrointestinal tract, peripheral nervous system, and certain brain regions, such as the hypothalamus [94], and the CCK2 receptor (CCK2R), which is primarily expressed in the brain, and specific areas of the gastrointestinal tract, such as gastric epithelial parietal cells [94]. Due to their co-localizations in the gastrointestinal tract and the brain, CCKRs play a crucial role in regulating various physiological and cognitive functions, including digestion, emotion regulation, nociception, and memory [95]. A study in rats showed that an activated CCK system had an anti-inflammatory activity [96]. A reduction in CCK activity is shown to disrupt the Gut-Brain axis through inflammation induction, whereas CCK pretreatment prevents gut permeability induced by LPS [96] (Fig. 2).

Of interest, ART success rate is lower in Western-like diet-consuming group compared to controls, as indicated by the weak response to ovulation initiation and a greater requirement of higher doses of gonadotropins and extended rounds of treatments for proper follicular development [97–99]. Overall, these studies suggest that WD can have a negative impact on the gut microbiota and gut-brain axis, which may exacerbate infertility in women. Adopting a healthier diet that is high in fiber and low in saturated fat and sugar, such as MD, may help restore the balance of the gut microbiota and improve fertility outcomes in women (Fig. 1).

The impact of the Mediterranean Diet and single nutrients on MGB axis in infertile women

In contrast to WD, MD is characterized by high consumption of fruits, vegetables, whole grains, olive oil, fish, and nuts while minimizing red meat, processed foods, and sugary beverages [100]. Researchers have extensively studied the positive impacts of the MD on various diseases, including female infertility. Two key pathophysiological mechanisms related to inflammation and oxidative stress were identified as major contributors to female infertility and ART failure (Table 1). MD is rich in anti-inflammatory food such as oleuropein, a

natural extract and polyphenol enriched in olive oil and olive leaves. Park, Yuri et al. [101] surgically induced endometriosis in C57BL/6 female mice. This condition is usually treated by oral contraceptives or GnRH agonists. In their study, they suggested oleuropein as a non-hormonal treatment and a nutraceutical therapy that can significantly reduce the levels of cytokines (Csf3, Csf1, Ccl2, Sicam1, Il1rn, etc.) in endometriotic lesions by inhibiting Erβ as shown by the effective suppression of ERβ nuclear translocation induced by E2 in human endometrial cells [101]. Moreover, oleuropein enhanced the pregnancy rate (100%) as shown by the fertility assay [101]. Interestingly, *Lactobacillus*, *Bifidobacteria* and *Enterococcus* genera hydrolyze oleuropein into hydroxytyrosol, a polyphenol with antioxidant, anti-inflammatory and immuno-modulatory roles.

Antioxidants improve oocyte quality by mitigating oxidative stress from ROS generated by mitochondrial respiration [102]. For instance, mitochondrial dysfunction has been identified in the pathogenesis of PCOS, characterized by reduced mitochondrial O2 consumption and glutathione (GSH) levels, a potent antioxidant accompanied by increased ROS levels [103]. A low antioxidant status in the peritoneal fluid was also observed in cases of idiopathic infertility. The latter is possibly explained by higher levels of ROS, which are thought to be associated with decreased levels of antioxidants such as GSH and vitamin E [103]. MD, on the other hand, is abundant in antioxidants (e.g., myricitrin), vitamins, and minerals, so it could reverse these effects.

It is known that aging implies greater oxidative stress. In this perspective, a study conducted by Omidi, Mina et al. [104] investigated the effects of myricitrin, a glycoside found in the fruits, branches, bark, and leaves of plants, in addition to vitamin E on the fertility of female mice in D-galactose (D-gal) aging model. Their results indicated a significant decrease in the hormonal levels of LH and FSH and an increase in estrogen and progesterone levels in D-gal-treated mice supplemented with myricitrin and vitamin E compared to D-gal-treated mice [104].

MD is also characterized by a high intake of plant-based foods, particularly those rich in fibers, which promote the growth of beneficial bacteria such as *Akkermansia muciniphila* [105]. This bacterium is associated with a healthy gut lining, improved metabolic health, and reduced inflammation [106]. As a next-generation probiotic microorganism, *Akkermansia muciniphila* plays a crucial part in supporting brain functions through the MGB axis. Moreover, it holds promise as a potential treatment target for various neuropsychological disorders [107].

MD has been associated with improved ovarian function, higher success rates of ART procedures, and a reduced risk of developing PCOS. These effects can be attributed to the high intake of fibers and the production of microbial metabolites [108]. A study conducted by De Filippis, et al. [109] detected an increase in the levels of fecal SCFAs, *Prevotella* bacterium, and other fiber-degrading Firmicutes when following MD, whereas low adherence to MD was associated with higher TMAO levels. In another study [110], Rodriguez Paris et al. used a dihydrotestosterone (DHT)-induced PCOS-like mice model to show the effects of macronutrient energy balance (15–20% protein, 35–40% carbohydrate and 35–45% fat), resembling that of an MD, on increasing microbial diversity [110] and rescuing the ovulatory dysfunction phenotype in the PCOS mouse model [111].

In light of the high levels of SCFAs in the MD, gut microbiota-derived SCFA have been shown to have neuroprotective effects [112] through the activation of the transcriptional machinery that controls the expression of brain-gut peptides through G protein-coupled receptors [113]. Recently, the emerging role of brain-gut peptides in understanding the crosstalk between the gastrointestinal system and the central nervous system has garnered increased attention due to its potential implications for both physical and mental health. Brain-gut peptides or mediators are hormones, neurotransmitters, or other signaling molecules secreted by enteroendocrine cells (EEC) that interact with immune system cell receptors and afferent fibers of the vagus nerve within the gut [114]. Subsequently, they can enter the systemic circulation and have the potential to modulate appetite, mood, or anxiety [114]. These gut-brain mediators include glucagon-like peptide 1 (GLP-1), CCK, corticotropin-releasing factor (CRF), GABA, growth hormone releasing peptide (ghrelin) and peptide YY (PYY) [115]. A study by Thombare, Ketan et al. provided evidence on how the secretion of GLP-1, a hormone and a neurotransmitter released by enteroendocrine L-cells of the gastrointestinal (GI) tract and CNS, is stimulated by dietary factors. The researchers showed that unsaturated fatty acid (18:1) oleate increases GLP-1 secretion by GLUTag cells, on the other hand, they found an opposing effect on GLP-1 levels in the presence of saturated fatty acid (16:0) palmitate, which was shown to induce apoptosis of GLP-1-secreting GLUTag cells [116].

Various studies have investigated the anti-inflammatory role of GLP-1 in the case of obesity-related reproductive disorders and PCOS, demonstrating its protective effects against metabolic stress in the ovaries and endometrium [117–119]. GLP-1 receptor agonists (GLP-1 RAs) have proven to be effective as monotherapy or in combination with metformin for obese females with PCOS, leading to weight reduction, menstrual period regulation, and decreased testosterone levels, thereby improving fertility and pregnancy rates [120]. Studies have also shown that GLP-1 RAs can alter gut microbiota composition,

increasing levels of beneficial genera like *Lactobacillus* and *Akkermansia*, while reducing pathogenic species like *Enterobacteriaceae* [121]. At the same time, GLP-1 could also potentially provide beneficial effects on certain symptoms commonly observed in psychiatric disorders, including depression and anxiety [114, 122]. In a group of patients with mood disorders and cognitive deficits, a 4-week treatment with a GLP-1 agonist was observed to reverse the cognitive deficits without impacting metabolic parameters [123]. The results indicate that targeting GLP-1 could potentially provide beneficial effects on certain symptoms that may be more commonly observed in psychiatric disorders, including depression and anxiety [114, 122]. Moreover, a reduction in the risk of depression, anxiety and stress was observed in relation to higher adherence to MD, compared to a lower adherence, following a dose-response pattern [124].

In addition, MD has been associated with favorable changes in insulin resistance, metabolic disturbances, and obesity risk, which are risk factors for infertility [125, 126]. These improved effects have been shown to positively impact the success rate of IVF [127]. A large study involving 2,527 infertile women participating in the Nurses' Health Study II showcased the effect of nutrition on female reproductive health and fertility. This study pointed out a 92% increase in the risk of ovulatory infertility in women consuming high glycemic index diet compared to those consuming a low glycemic index diet. Conversely, adherence to daily multivitamin intake showed a 41% decrease in ovulatory infertility [128, 129]. Moreover, the study showed that the intake of protein from vegetable sources was associated with improved fertility, while the consumption of protein from animal sources was associated with infertility attributed to anovulation [129].

Vitamins are a class of micro-organic substances only from food that maintain some vital physiological activities and functions in the human body. Although they do not provide energy, they regulate metabolic processes. Many vitamins play a key role in supporting female health, such as vitamins B, C, D, E, and some coenzymes [130]. Due to the expression of vitamin D receptors (VDRs) in the female central and peripheral organs of reproduction, the role of Vitamin D in infertility is highly investigated [131–134]. VDRs are also localized in brain structures such as the hypothalamus and the pituitary gland, suggesting an effect of vitamin D levels on the HPO axis [132, 135]. Vitamin D intake can improve fertility by regulating the menstrual cycle and follicular development [136], whereas its deficiency is reported to be highly associated with PCOS-related infertility, altered HPO axis, and ovulation disorders [135, 137]. A possible mechanism by which Vitamin D deficiency can disturb the HPO axis is through the reduction of silent information regulator 1 (SIRT1) and other antioxidants, which can consequently induce inflammation, increase ROS levels, lead to mitochondrial dysfunction, and promote female infertility [138]. Vitamin E, which is an antioxidant, has shown a promising role in improving fertility by reducing inflammation in the female reproductive system [139] and protecting against the deleterious effects of ethanol on the altered hormonal levels of the HP-gonadal axis [140].

Polyunsaturated fatty acids (PUFA) are also essential nutrients for the female reproductive system that have anti-inflammatory properties that may help to reduce oxidative stress and increase progesterone levels, leading to a lower risk of anovulation and improved fertility [141]. Carisha S et al. investigated the pro-inflammatory effects of low omega-3 (n-3) PUFA levels such as, including docosahexaenoic acid (DHA), on 1789 women from the Netherlands Study [142]. Their results have indicated an association between dysregulated HPA stress system markers and elevated inflammatory markers, such as C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α), with lower n-3 PUFA plasma levels [142]. Others have suggested that omega-3 supplementation may improve fertility in women undergoing ART [46]. Folate, a B-group vitamin, is an essential nutrient for a healthy female reproductive system due to its crucial role during fetal development, preventing neural tube defects [143]. It also plays a role in ovulation and can improve fertility by enhancing cognitive function and mood. Iron is important for producing red blood cells and can help to prevent anemia and reduce symptoms of depression and anxiety, which in turn can affect ovulation [144]. Foods high in iron include red meat, poultry, seafood, beans, and leafy green vegetables.

In conclusion, several nutrients have been identified as having an impact on the MGB axis and fertility in both infertile women and women undergoing ART. A balanced and varied diet rich in nutrients may help improve reproductive health and increase the chances of successful conception.

Discussion

Diet composition impacts the human body at different molecular, cellular, biological, and physiological levels. Interestingly, WD and MD are two dietary patterns suggested to play a detrimental or therapeutic role, respectively, in different diseases. Similarly, in the case of female infertility, many studies were interested in exploring how these dietary patterns could improve or aggravate the symptoms associated with infertility. The contrasting effects of WD and MD on fertility are evident, with WD exacerbating inflammation, hormonal imbalance, and gut dysbiosis, while MD mitigates these issues through its anti-inflammatory and nutrient-dense profile.

Our review has outlined and illustrated the cellular and molecular mechanisms by which the WD and MD affect female fertility. A research study by David et al. [145] has demonstrated that WD decreases the microbial diversity in the gut, increasing the growth and activity of *Bilophila wadsworthia*, which in turn is associated with inflammatory bowel disease (IBD) due to its role in inducing the inflammation of intestinal tissue through the production of hydrogen sulfide (H_2S) [146]. Gut dysbiosis triggered by WD promotes a pro-inflammatory environment, marked by increased levels of LPS secreted by Gram-negative bacteria [147] (Fig. 2). LPS triggers systemic inflammation and is implicated in endometriosis, which can compromise fertility [148, 149]. Additionally, obesity, a consequence of the WD, disrupts hormonal balance through multiple pathways [150]. For example, increased adipose tissue secretes adipokines, including leptin, and cytokines that inhibit GnRH secretion and interfere with the HPO axis, leading to menstrual irregularities and reduced fertility [151, 152].

In contrast, MD has been demonstrated to improve obesity, lipid profile, and inflammation. These changes may be mediated by the diet-derived increase in *Lactobacillus*, *Bifidobacterium*, and *Prevotella*, and the decrease in *Clostridium* [153–156]. Moreover, the production of SCFA, mainly due to the adherence to MD, promotes the synthesis and secretion of PYY and GLP-1 by enteroendocrine L-cells [157], and the activation of the CCK system due to the consumption of dietary fiber [93]. PYY signaling has modulatory properties that involve neuroprotection against neurological diseases and psychiatric disorders [114]. On the other side, the low adherence to the MD was associated with elevated urinary TMAO [109]. Furthermore, the adherence to a plant-based MD, or "green" MD, by daily consuming green tea and a leafy vegetable called Mankai was shown to induce a two-fold increase in fasting ghrelin levels compared to following a traditional MD [158]. The secretion of ghrelin can regulate the HPO axis activity by decreasing excess pituitary-secreted LH levels in PCOS patients [159, 160]. Moreover, *Clostridium* and *Ruminococcus* were reported to be positively associated with ghrelin, whereas increased *Bacteroidetes/Firmicutes*, *Faecalibacterium*, and *Prevotellaceae* were negatively associated with ghrelin [161]. Conversely, chronic exposure to HFD exerts negative feedback on ghrelin production and secretion in both animal and human studies [162].

The potential mechanism is depicted in Fig. 2. Recent studies showed that a diet based on MD recommendations positively affects mental and physical health [163, 164]. Additionally, probiotic supplementation is a promising approach. A study conducted by Zhang, J. et al. [32] revealed the potential benefits of consuming the probiotic *Bifidobacterium lactis* V9 once daily for 10 weeks on gut microbiome composition and gut-brain meditators' levels in PCOS patients. The authors reported that the probiotic supplementation in PCOS patients significantly induced the growth of SCFA-producing microbes, including *Faecalibacterium*, *Butyricimonas*, and *Akkermansia*, in the gut microbiome of patients. These patients noticed an increase in the levels of gut-brain mediators (ghrelin and PYY) as well as a dramatic reduction in FSH and LH levels [32].

Despite these insights, the previous studies have notable limitations including reliance on self-reported dietary intake, which is prone to recall bias and inaccuracies. Sample sizes in some studies are small, reducing the generalizability of the findings. Furthermore, limited longitudinal data restricts the ability to assess the long-term effects of WD on reproductive outcomes. Moreover, cultural preferences, socioeconomic constraints, and limited access to healthy food options can pose significant barriers to adopting the MD and avoiding reliance on WD, highlighting the need for tailored dietary interventions that consider these factors. The link between gut microbiota, brain chemistry, and infertility is an intriguing area of research. However, this field is still in its infancy. More longitudinal studies and clinical trials are needed to explore how the food we consume and other dietary patterns, including the ketogenic diet, can impact the communication between the gut and the brain, which in turn may have implications for infertility. These studies will help elucidate the underlying mechanisms and aid in planning specific and personalized dietary approaches.

Conclusions

In this review, we discussed the principles of gut microbiota brain axis alterations with a focus on the distinct effects of the Western and Mediterranean diets, as well as various nutrients, on the management of female infertility. We highlighted the need to further explore the potential detrimental or therapeutic effects of Western and Mediterranean diets, respectively, and the importance of standardizing dietary formulations in order to ensure the reproducibility of clinical trials. While research in this area is ongoing and more studies are needed to establish definitive connections, maintaining a healthy diet and gut microbiome could potentially benefit subfertile women. A balanced diet rich in fiber, prebiotics, and probiotics, along with appropriate lifestyle changes, may positively influence the gut-brain axis and contribute to improved reproductive outcomes. In the era of personalized medicine and due to the complex nature of infertility, advances in our understanding of these emerging areas are fascinating and open new horizons in the management of infertile couples.

Abbreviations

ASRM	American Society of Reproductive Medicine
ART	Assisted reproductive technology
BA	Butyric acid
CRP	C-reactive protein
CNS	Central nervous system
CCK	Cholecystokinin
CAH	Congenital adrenal hyperplasia
CRF	Corticotropin-releasing factor
DHA	Docosahexaenoic acid
EEC	Enteroendocrine cells
E2	Estradiol
FSH	Follicle-stimulating hormone
GLP-1	Glucagon-like peptide 1
GSH	Glutathione
GnRH	Gonadotropin-releasing hormone
HFD	High-fat diet
hCG	Human Chorionic Gonadotropin
HPO	Hypothalamic-pituitary-ovarian
IVF	In vitro fertilization
LPS	Lipopolysaccharide
LH	Luteinizing hormone
MD	Mediterranean diet
MGB	Microbiota-gut-brain axis
PHQ-9	Patient Health Questionnaire-9
PYY	Peptide YY
PCOS	Polycystic ovary syndrome
PUFA	Polyunsaturated fatty acids
PGCs	Porcine granulosa cells
P4	Progesterone
ROS	Reactive Oxygen Species
SCFAs	Short-chain fatty acids
SIRT1	Silent information regulator 1
TMA	Trimethylamine
TMAO	Trimethylamine N-oxide
TNF-α	Tumor necrosis factor-alpha
VDRs	Vitamin D receptors
WD	Western Diet
WHO	World Health Organization
gmGUS	β-glucuronidase
GABA	γ-aminobutyric acid

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