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## Review Article

# Gene–Nutrient–Lifestyle Interactions in Female Infertility: Unravelling the Vitamin D–PCOS–Metabolic Axis: An In-Depth Review

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## Abstract

Female infertility, along with the decline of fecundity, is an alarming health concern of the modern era, which is predominantly contributed to by an unhealthy lifestyle, such as sedentary behavior and the consumption of junk food. Anovulation and reduced number and quality of oocytes are prevalently associated with polycystic ovary syndrome (PCOS) and endometriosis, which can lead to reproductive health complications. A large number of global populations engage in a dormant lifestyle and prefer inadequate physical activities, which cause a reduction in reproductive fitness by impairing protein transporter activities and increasing muscle glucose levels.

Vitamin D deficiency (VDD) is linked to female infertility, such as PCOS, particularly through its impact on reproductive hormones and ovarian function. Research shows stronger associations in conditions like PCOS, a common cause of infertility.

Junk food, containing a high amount of simple sugar and saturated fat, can lead to obesity and insulin resistance, emerging features of reproductive failure, by abnormally modulating the metabolism of carbohydrates and lipids. Optimum exercise and a restricted, healthy diet can modulate molecular, metabolic, and physiological activities, which can reduce the severity of reproductive disorders and rejuvenate fertility outcomes.

In this review article, the modulatory effects of a sedentary lifestyle and consumption of unhealthy junk food, highlighting the underlying molecular mechanisms of female reproductive disorders, have been narrated.

## Introduction

Female infertility is a multifactorial reproductive disorder clinically characterized by the inability to achieve conception after 12 months of regular, unprotected sexual intercourse, reflecting complex disturbances in endocrine, metabolic, genetic, and reproductive physiology [1]. Among the major causes of female infertility, ovulatory dysfunction accounts for nearly 85% of cases and is strongly influenced by sedentary lifestyle and excessive junk food consumption [1,2]. These factors adversely affect fecundity, the biological capacity for reproduction, which is essential for maintaining reproductive homeostasis across populations [3]. Reduced fecundity may

arise not only from impaired reproductive capacity but also from altered reproductive behaviour and lifestyle patterns [3]. Studies have consistently shown that most ovulatory disorders characterized by anovulation and hyperandrogenism are closely associated with polycystic ovary syndrome (PCOS) [4,5]. In addition, obesity, unhealthy dietary habits, environmental pollutants, and toxin exposure negatively influence both the number and quality of oocytes, thereby compromising fertility [6]. Emerging evidence further suggests that sedentary behaviour and inadequate dietary intake of vitamin D contribute significantly to vitamin D deficiency (VDD)-associated PCOS manifestations [7,8]. According to the World Health Organization (WHO), nearly one in six



individuals of reproductive age experiences infertility globally, with ovarian, uterine, tubal, and endocrine abnormalities representing major contributors in women [6]. Moreover, chromosomal abnormalities such as monosomy X, deletions, duplications, and imbalanced X-autosome rearrangements can result in premature loss of primordial oocytes and gonadal dysgenesis [9]. Impaired granulosa cell signalling and skewed X-chromosome inactivation (XCI) may also contribute to primary ovarian insufficiency through accelerated germ cell depletion [9].

Modern lifestyle transitions have markedly increased physical inactivity worldwide, with nearly one-third of the global population avoiding regular physical activity [10]. Urbanization, prolonged office work, social media dependence, and lack of exercise-friendly environments have collectively promoted sedentary behaviour [10–16]. Such inactivity disrupts metabolic homeostasis by reducing protein transporter activity, impairing lipid metabolism, decreasing lipoprotein lipase activity, and altering the insulin-like growth factor (IGF) axis, ultimately lowering insulin sensitivity [10]. Sedentary behaviour additionally increases hypertension, cardiac workload, and vascular dysfunction through alterations in sympathetic nervous system activity [10–13]. Accumulating evidence indicates that restricted skeletal muscle movement and chronic inactivity significantly reduce conception potential [2,17–20]. In contrast, moderate-to-vigorous physical activity improves cardiovascular health, insulin sensitivity, mental well-being, ovulation, pregnancy outcomes, and ovarian endocrine function [2,21–25]. Exercise enhances endothelial nitric oxide synthase (eNOS) activity, improves circulation, and activates adenosine monophosphate kinase (AMPK), thereby stimulating fatty acid oxidation, improving metabolic balance, and enhancing reproductive health [9–16]. Junk food consumption has emerged as another major lifestyle-associated contributor to female reproductive dysfunction. Foods rich in refined sugar, saturated fat, cholesterol, and salt stimulate dopamine-mediated reward pathways, promoting addictive eating behaviour [11–14]. However, their excessive intake adversely affects metabolic and reproductive health. High glycaemic load diets and saturated fats contribute to obesity, insulin resistance, and endocrine imbalance while simultaneously depriving the body of essential nutrients [11]. Such dietary patterns are strongly associated with menstrual irregularities, dysmenorrhea, obesity, diabetes, and PCOS-related infertility [12,13]. Furthermore, junk food disrupts hormonal regulation by impairing hypothalamic-pituitary-ovarian axis (HPOA) signalling [12,13]. Nutritional imbalance, fasting, and reduced intake of proteins and essential amino acids also influence nutrient-sensing pathways, including forkhead-box-O (FOXO) transcription factors, which play crucial roles in metabolic regulation and reproductive longevity [14,26–28]. Overall, the growing interaction among sedentary lifestyle, junk food consumption, metabolic dysfunction, VDD, and PCOS highlights the urgent need for lifestyle-based preventive and therapeutic strategies to improve female reproductive health.

## Rationale and scopes of the review

Despite growing evidence on the role of lifestyle factors in reproductive health, there remains a lacuna of guidelines, and personalised-tailored recommendations for physical activity and dietary interventions exist according to the baseline fitness level of patients, health status, and infertility-related diagnosis for the management and mitigation of infertility. Moreover, existing studies often focus on isolated aspects rather than providing an integrative understanding of molecular, physiological, and clinical interactions. These gaps hinder healthcare providers from offering clear, evidence-based recommendations on optimal exercise intensity, frequency, and dietary patterns to maximize conception rates. Therefore, this review aims to comprehensively analyse the impact of sedentary lifestyle and junk food consumption on female fertility, highlighting mechanistic pathways, clinical implications, and potential therapeutic strategies by highlighting the intricacy of VDD-PCOS crosstalk from our previous study outcomes.

## Methodology

### Literature search strategy

A systematic and comprehensive literature search was conducted across major scientific databases, including PubMed, ScienceDirect, and PubMed Central (PMC), to ensure broad coverage of relevant studies. The search strategy was designed to capture both experimental and observational research, as well as review articles, thereby providing a multidimensional understanding of the topic. Emphasis was placed on peer-reviewed publications to ensure the reliability and scientific validity of the included data.

### Keywords and time frame

The search incorporated specific keywords such as “female fertility,” “fecundity,” “sedentary lifestyle,” “junk food,” and “reproductive health,” combined using Boolean operators to refine results. The time frame spanned from January 2003 to March 2026, allowing inclusion of both foundational studies and recent advancements. This extensive temporal coverage facilitated the identification of evolving trends and emerging concepts in reproductive health research.

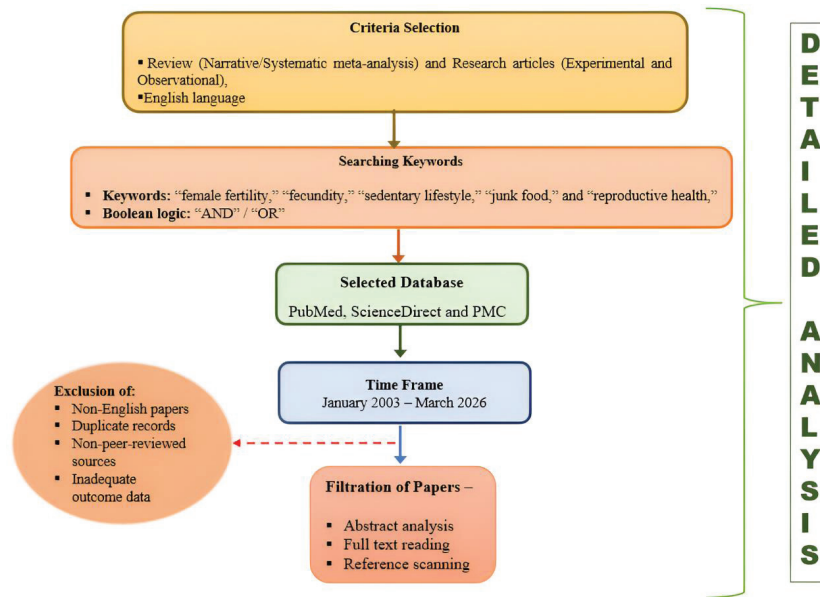
### Study selection

Studies were selected based on relevance to the topic, methodological rigor, and clarity of outcomes. Only articles published in English were included to maintain consistency in interpretation. Both human and mechanistic studies were considered to integrate clinical observations with molecular insights. This approach ensured a balanced and comprehensive synthesis of evidence (Figure 1).

## Discussion

### Reframing female infertility: beyond a linear model

Female infertility emerges through a complex interaction between endocrine imbalance, metabolic dysfunction, ovarian



**Figure 1:** Overview of systematic literature search and study selection process.

Panel 1 – Study types included: The search intentionally targeted multiple study designs narrated in English: experimental (in vitro, animal), observational (cohort, case-control, cross-sectional), and review articles. Emphasis on peer-reviewed publications increased confidence in methodological quality and reliability of reported findings. Both human clinical studies and mechanistic investigations were included to integrate clinical outcomes with underlying biological mechanisms.

Panel 2 – Search strategy and keywords: A comprehensive search strategy combined specific keywords – “female fertility,” “fecundity,” “sedentary lifestyle,” “junk food,” and “reproductive health” – using Boolean operators (AND, OR) to refine retrieval and capture both focused and related articles. The search was restricted to publications in English and spanned the period June 1998 to March 2026, permitting inclusion of foundational studies and recent advances.

Panel 3: Major scientific databases (PubMed, ScienceDirect, PubMed Central) were queried to ensure broad coverage of biomedical and life-science literature. These sources capture peer-reviewed primary research, reviews, and mechanistic studies relevant to reproductive health.

Left panel – Exclusion criteria duplicated records, non-peer-reviewed sources, and studies lacking adequate outcome data.

Panel 4 – Screening and inclusion criteria: Retrieved records were screened for relevance to the research question, methodological rigor (study design, sample size, controls), and clarity of outcomes. Inclusion criteria required English language and direct relevance to female reproductive outcomes or mechanistic pathways linking lifestyle/nutrition to fecundity.

impairment, genetic susceptibility, and environmental influences. Among the different etiological contributors, ovulatory dysfunction remains one of the most dominant causes of infertility, with PCOS representing the principal metabolic–endocrine disorder associated with chronic anovulation, impaired folliculogenesis, menstrual irregularities, and reduced fecundity. The evidence presented throughout this review strongly indicates that infertility in PCOS is not merely confined to ovarian pathology; rather, it represents a systemic metabolic disorder involving insulin resistance, hyperandrogenism, chronic inflammation, oxidative stress, altered adipokine signalling, and micronutrient imbalance. At the molecular level, hyperinsulinemia acts as a central pathogenic trigger in PCOS-associated infertility. Increased insulin levels stimulate ovarian theca cells, resulting in excessive androgen biosynthesis while simultaneously suppressing hepatic synthesis of sex hormone-binding globulin (SHBG), thereby increasing circulating free androgen concentrations. This hyperandrogenic milieu disrupts granulosa cell aromatase activity, impairs follicular maturation, and culminates in follicular arrest and chronic anovulation. Altered gonadotropin dynamics, particularly dysregulated luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion secondary to disrupted gonadotropin-releasing hormone (GnRH) pulsatility, further aggravate ovulatory failure [12,18,19,21–23,28,29].

The review additionally highlights that oxidative stress and chronic low-grade inflammation significantly contribute to reproductive dysfunction in PCOS. Increased generation of reactive oxygen species (ROS), mitochondrial dysfunction, and inflammatory mediators such as tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin-6 (IL-6) impair ovarian microenvironment integrity and compromise oocyte quality. These inflammatory alterations interfere with insulin signalling pathways and steroidogenic balance, thereby reinforcing endocrine dysfunction. Furthermore, impaired mitochondrial oxidative capacity reduces adenosine triphosphate (ATP) generation within oocytes, negatively influencing oocyte competence and reproductive potential. An important mechanistic aspect emerging from this review is the intricate relationship between VDD and PCOS pathophysiology. Vitamin D, through vitamin D receptor (VDR)-mediated transcriptional regulation, modulates genes associated with steroidogenesis, insulin signalling, and ovarian physiology, including CYP19 and CYP17 pathways. The findings summarized in this article strongly support the concept that VDD aggravates insulin resistance, dyslipidemia, altered anthropometric indices, and endocrine imbalance in PCOS individuals. In addition, VDR gene polymorphisms, particularly FokI and BsmI variants, appear to modulate susceptibility and phenotypic heterogeneity of PCOS, emphasizing a significant gene–nutrient interaction axis in female infertility. The association between VDD, anti-

Müllerian hormone (AMH), insulin resistance indices, and severity of PCOS manifestations further strengthens the role of vitamin D as both a biomarker and a potential therapeutic target. Consequently, infertility in PCOS should be interpreted as the result of continuous interactions among endocrine pathways, metabolic disturbances, micronutrient status, genetic predisposition, and environmental influences [21-25,29-37].

## Sedentary lifestyle: Molecular driver, not just a risk factor

### Physical activity: Metabolic, endocrine, and neurophysiological regulation of reproductive function

Regular physical activity plays a fundamental role in maintaining female reproductive health through its integrated effects on metabolic homeostasis, endocrine regulation, vascular physiology, and neuroendocrine balance. Exercise significantly improves insulin sensitivity, which is particularly important in women with metabolic disturbances such as PCOS, obesity, and insulin resistance-associated ovulatory dysfunction [38-42]. Improved insulin signalling reduces hyperinsulinemia-mediated ovarian androgen production, thereby lowering hyperandrogenism and restoring normal ovulatory cycles and follicular maturation [38-42]. In addition, physical activity promotes healthier body composition and reduces adiposity-related endocrine disturbances that adversely affect ovarian physiology and fertility potential [38-42]. Exercise also regulates gonadotropin dynamics by stabilizing the pulsatile secretion of GnRH, which is essential for balanced LH and FSH secretion during folliculogenesis [38-42]. Enhanced peripheral insulin sensitivity prevents excessive ovarian theca cell stimulation and reduces androgen biosynthesis, thereby improving granulosa cell activity and oocyte maturation [38-42]. Furthermore, exercise modulates adipokine signalling, particularly through increased adiponectin and improved leptin regulation, which contribute to anti-inflammatory effects, metabolic stability, and a healthier ovarian microenvironment [38-42].

At the molecular level, physical activity activates key metabolic pathways involved in cellular energy regulation and reproductive physiology. Exercise-induced activation of AMPK promotes fatty acid oxidation, improves glucose uptake, and enhances metabolic flexibility, thereby restoring endocrine balance and ovarian function [43,44]. Simultaneously, exercise stimulates eNOS, improving vascular function and ovarian blood circulation, which support follicular development, endometrial receptivity, and implantation potential [41,42,45,46]. Improved tissue perfusion additionally enhances oxygen and nutrient delivery to reproductive tissues, contributing to improved fertility outcomes. Physical activity further exerts protective effects through the regulation of oxidative stress and inflammatory pathways. Exercise promotes mitochondrial biogenesis via activation of peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1 $\alpha$ ), thereby improving oxidative metabolism and reducing ROS accumulation [47,48]. Reduced oxidative stress

preserves oocyte quality and follicular integrity. In parallel, regular exercise decreases pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6 while enhancing anti-inflammatory mediators, thereby reducing chronic low-grade inflammation associated with infertility and metabolic dysfunction [49,50]. Improved insulin receptor phosphorylation and activation of phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signalling pathways further strengthen insulin responsiveness and ovarian metabolic regulation [51].

### Physical activity and psychological benefits

Beyond metabolic and endocrine regulation, exercise significantly influences psychological and neuroendocrine health, both of which are closely linked with reproductive function. Infertility is frequently associated with anxiety, depression, stress, and reduced quality of life. Physical activity improves emotional well-being through exercise-induced release of endorphins and brain-derived neurotrophic factor (BDNF), which enhance mood, cognitive function, and stress resilience [45]. Regular exercise also reduces cortisol levels and normalizes hypothalamic-pituitary-adrenal axis (HPAA) activity, thereby counteracting stress-induced suppression of GnRH pulsatility and ovulatory dysfunction [33,40,52]. Furthermore, exercise enhances serotonergic and dopaminergic signalling, improving emotional regulation and reducing infertility-associated psychological burden [53,54]. Improved sleep quality and stabilization of circadian rhythms associated with regular physical activity additionally influence melatonin secretion, antioxidant defense, and hormonal synchronization essential for reproductive cyclicity and oocyte quality [55,56].

### Experimental and clinical evidence supporting exercise in fertility improvement

Experimental, observational, and clinical studies consistently support the beneficial role of physical activity in improving female reproductive health and fertility outcomes [56-65]. Randomized controlled trials (RCTs) demonstrate that structured exercise interventions significantly improve ovulation rates, menstrual regularity, endocrine balance, and pregnancy outcomes, particularly among overweight women and individuals with PCOS [56-58]. Improved insulin sensitivity and reduction of hyperinsulinemia-driven androgen excess appear to be major mechanisms underlying restoration of ovulatory function in these populations [38-40]. Clinical investigations further indicate that exercise-mediated improvements in adiposity, inflammatory status, vascular function, and hormonal balance collectively enhance follicular development, endometrial receptivity, and implantation success [41,42]. Longitudinal lifestyle intervention studies also reveal that combining exercise with dietary modification produces superior improvements in insulin sensitivity, metabolic stability, ovulatory function, and reproductive outcomes compared with isolated interventions alone [60-65]. These findings strongly support the concept that reproductive dysfunction is closely linked with modifiable metabolic and lifestyle-associated factors. Experimental evidence additionally highlights the importance of exercise-induced mitochondrial adaptation and oxidative stress regulation in

ovarian physiology. Enhanced mitochondrial function and reduced ROS accumulation improve oocyte competence and protect reproductive tissues from oxidative damage associated with obesity, insulin resistance, and chronic inflammation [47-50]. Studies examining molecular signalling pathways further demonstrate that exercise modulates AMPK and PI3K/Akt signalling, both of which are critically involved in steroidogenesis, glucose metabolism, follicular survival, and ovarian endocrine regulation [37-45] [43-51].

Psychological and neuroendocrine studies similarly support the beneficial impact of exercise on fertility. Reduction in stress, anxiety, and depressive symptoms following regular physical activity has been associated with improved HPOA regulation and restoration of reproductive endocrine balance [68-70]. Exercise-induced normalization of cortisol secretion and circadian rhythm stability may therefore indirectly enhance ovulatory function and fertility outcomes [33,40,55,56].

However, existing evidence also emphasizes that the reproductive effects of exercise follow a dose-dependent relationship. Moderate-intensity aerobic activity appears most beneficial, whereas excessive exercise, prolonged endurance training, or severe caloric restriction may induce hypothalamic suppression, luteal phase defects, and functional hypothalamic amenorrhea [59-61]. Energy deficiency states associated with excessive physical exertion disrupt GnRH pulsatility and ovarian hormonal regulation, ultimately impairing ovulation and fertility [60,61]. Variability in reproductive outcomes across studies further suggests that factors such as baseline body mass index (BMI), metabolic status, age, and hormonal profile significantly influence individual responses to exercise interventions [60-65].

Collectively, current evidence establishes physical activity as a major protective regulator of female reproductive health. Through coordinated metabolic, endocrine, inflammatory, vascular, mitochondrial, and neuropsychological mechanisms, regular moderate exercise improves ovarian physiology, hormonal balance, ovulation, implantation potential, and fertility outcomes. These findings reinforce the importance of individualized and precision-based lifestyle interventions in reproductive medicine, particularly for women affected by PCOS and lifestyle-associated metabolic dysfunction (Table 1) [56-65].

## Junk food, fast food, and ultra-processed diets: impact on female reproductive health

### Neuroendocrine, metabolic, and molecular disruption of reproductive function

Frequent consumption of junk food, fast food, and ready-to-eat ultra-processed diets has emerged as a major lifestyle-associated contributor to female reproductive dysfunction and infertility. These dietary patterns, characterized by excessive intake of refined sugars, saturated fats, trans fats, sodium, food additives, and calorie-dense nutrient-poor ingredients, profoundly disturb endocrine, metabolic, inflammatory, and neurophysiological pathways essential for normal reproductive

function [66-72]. Evidence increasingly suggests that unhealthy dietary behaviour does not merely coexist with infertility-related disorders but actively participates in the pathogenesis of ovulatory dysfunction, menstrual irregularities, and PCOS-associated reproductive impairment [12,18,21-23,28]. One of the central mechanisms linking junk food consumption with infertility is the development of insulin resistance and chronic hyperinsulinemia. High glycaemic load diets induce repeated insulin surges that stimulate ovarian theca cells to produce excessive androgens while simultaneously suppressing hepatic synthesis of SHBG, thereby increasing circulating free androgen levels [12,18,21-23,28]. This hyperandrogenic environment disrupts follicular maturation, impairs granulosa cell function, and promotes follicular arrest and chronic anovulation, which are hallmark features of PCOS-associated infertility [12,18,21-23,28]. In addition, altered GnRH pulsatility and disruption of hypothalamic-pituitary-ovarian axis (HPOA) regulation further destabilize ovulatory cyclicity and menstrual function (Table 2) [66-68].

At the molecular level, junk food consumption profoundly alters nutrient-sensing and metabolic regulatory pathways involved in reproductive physiology. Excessive caloric intake and poor-quality diet dysregulate AMPK, mechanistic target of rapamycin (mTOR), forkhead box O (FOXO), and fibroblast growth factor 21 (FGF21) signalling pathways, all of which coordinate cellular metabolism, oxidative stress responses, aging, and ovarian function [73-78]. AMPK normally functions as a cellular energy sensor that promotes metabolic balance and preserves cellular integrity under low-energy conditions, whereas excessive nutrient availability and overactivation of mTOR signaling promote metabolic imbalance and ovarian dysfunction [76-78]. FOXO transcription factors play critical roles in oxidative stress resistance, apoptosis regulation, and maintenance of oocyte quality, while FGF21 contributes to systemic energy homeostasis and reproductive adaptation during metabolic stress [57-62] [73-78]. Dysregulation of these interconnected pathways disrupts the balance between metabolism and reproduction, thereby accelerating reproductive decline and infertility progression [76-78]. Chronic intake of ultra-processed food also promotes oxidative stress and systemic inflammation through accumulation of advanced glycation end-products (AGEs), lipid overload, and inflammatory activation [66-72,79-82]. Increased production of ROS damages ovarian tissues, impairs oocyte quality, and compromises follicular microenvironment integrity [34,35]. Simultaneously, visceral adiposity associated with unhealthy dietary behaviour acts as an endocrine organ that secretes pro-inflammatory cytokines such as TNF- $\alpha$ , IL-6, and resistin, which interfere with insulin receptor signalling and ovarian steroidogenesis [34,35,83,84]. This chronic inflammatory state aggravates endocrine dysfunction, hyperandrogenism, and ovulatory failure while reducing implantation success and fertility potential (Figure 2) [34,35,83,84].

### Infertility and gut dysbiosis

Emerging evidence identifies gut microbiota dysbiosis as a major mechanistic link between unhealthy dietary behaviour,



**Table 1:** Effects of physical activity on female reproductive health

Assessment of physical activity	Study design	Finding(s)	Possible mechanism(s)	Reference(s)
Vigorous to mild exercise controlled caloric intake to calorie deficit	Randomized controlled trial (premenopausal eumenorrheic women, n=34)	Moderate and severe energy deficit leads experienced luteal phase defect of menstrual cycles (85%) and anovulation (35%)	<ul style="list-style-type: none"> <li>• Lowers circulating insulin, leptin, and glucose, while elevating cortisol and ghrelin.</li> <li>• Hypoleptinemia (low leptin) and low insulin reduce anabolic "energy-sufficient" signaling and activate stress-related pathways (e.g., via hypothalamic AMPK, NPY/AgRP neurons).</li> </ul>	[62]
Sedentary women and active runners running	Cross-sectional study (eumenorrheic women, n=35)	In 9% of sedentary group luteal phase was defective	<ul style="list-style-type: none"> <li>• Impaired LH support to the CL can result in reduced P4 output.</li> <li>• In active runners, LPD is often linked to relative energy deficiency (low energy availability), which suppresses GnRH pulsatility and reduces LH, thereby impairing luteal P4 synthesis.</li> </ul>	[63]
Physical activity lowers the likelihood of infertility.	Comprehensive systematic review and meta-analysis	An inverse correlation between varying levels of physical activity and infertility. A moderate to high level of physical activity significantly decreased the overall risk of infertility, identifying this level of physical activity as a prevalent protective factor.	<ul style="list-style-type: none"> <li>• Moderate-to-high physical activity may reduce infertility by lowering inflammatory cytokines and oxidative stress markers, while boosting antioxidant defenses; this helps protect gametes and the reproductive environment needed for conception.</li> <li>• It may also normalize hypothalamic-pituitary-ovarian axis signaling by improving gonadotropin regulation and, in women with anovulation or PCOS, reducing insulin and androgen excess so ovulation can resume.</li> </ul>	[64]
A 4-month exercise program with a physical therapist (Tailored: content, and frequency)	Randomized parallel design (n=43), PCOS women (overweight or obese)	Higher (65%) ovulatory rate and spontaneous pregnancy (35%) in the exercise group	<ul style="list-style-type: none"> <li>• Regular moderate exercise improves insulin sensitivity and reduces fasting insulin and free androgens, particularly in overweight/obese women and those with PCOS-like phenotypes.</li> <li>• Lower insulin and androgens decrease ovarian hyper-stimulation and follicular atresia, allowing more follicles to reach the pre-ovulatory stage and respond appropriately to gonadotropin-releasing hormone (GnRH) pulses.</li> </ul>	[65]

AMPK=adenosine monophosphate-activated protein kinase, NPY=neuropeptide Y, AgRP=agouti-related peptide, LH=luteinizing hormone, CL=corpus luteum, P4=progesterone, LPD=luteal phase defect, PCOS= polycystic ovary syndrome.

**Table 2:** Effects of junk food on female reproductive health

Assessment of junk food	Study design	Finding(s)	Possible mechanism(s)	Reference(s)
High consumption of ultra-processed foods is associated with female infertility	Cross-sectional study (n=3060) in National Health and Nutrition Examination Survey	Among women of reproductive age, a high intake of ultra-processed foods is linked to female infertility. Body mass index (BMI) serves as a mediator in the relationship between ultra-processed foods consumption and female infertility.	<ul style="list-style-type: none"> <li>• Endocrine disruption: Ultra-processed foods may increase exposure to packaging- and processing-related chemicals such as phthalates and bisphenol A, which can disrupt hormone signaling needed for ovulation and implantation.</li> <li>• BMI-mediated metabolic effects: Higher ultra-processed food intake can promote weight gain and adverse metabolic changes, and BMI may partly mediate infertility by altering insulin sensitivity, inflammation, and reproductive hormone balance.</li> </ul>	[69]
The relationship between the consumption of junk food and the body mass index of adolescent girls, as well as the associated menstrual irregularities, will be examined and compared with a control group.	Cross-sectional study (n=200)	The intake of junk food has a detrimental impact on the menstrual cycle; however, further research is required to validate the correlation between BMI, the consumption of salty snacks, and frozen meat products with menstrual irregularities.	<ul style="list-style-type: none"> <li>• Insulin resistance → altered ovarian steroidogenesis: Diets high in refined sugars and saturated/trans fats (common in junk food) raise insulin and promote insulin resistance, which stimulates ovarian theca cells to increase androgen production and alters granulosa cell function, disrupting the estradiol/progesterone balance and causing irregular follicular development and menstrual cycle disturbances.</li> <li>• Inflammation and disrupted hypothalamic-pituitary signaling: Excessive saturated fats and ultra-processed components increase systemic inflammation (proinflammatory cytokines) and oxidative stress, which can impair hypothalamic GnRH pulsatility and pituitary FSH/LH secretion, and can also affect endometrial responsiveness to progesterone – together producing irregular cycles, and dysmenorrhea.</li> </ul>	[70]



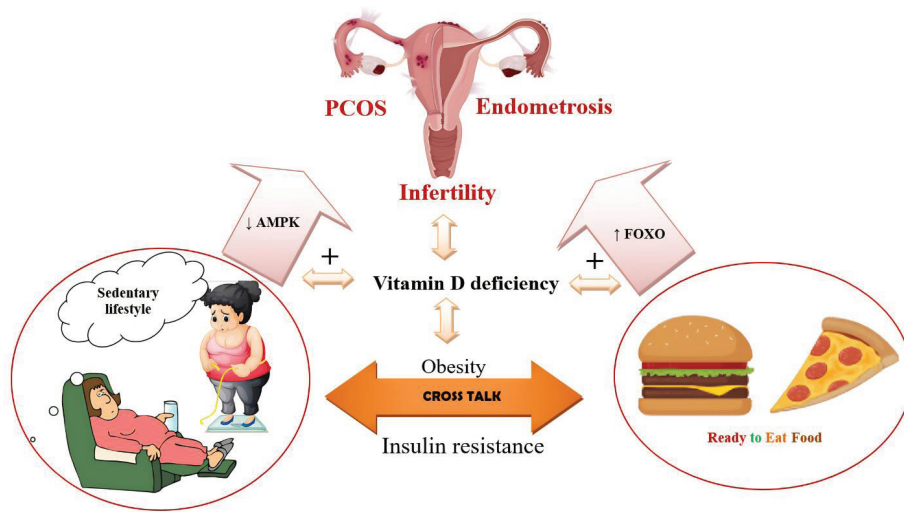
<p>Skipping breakfast</p>	<p>Questionnaire survey (n=315)</p>	<p>Menstrual disorders in young college students</p>	<ul style="list-style-type: none"> <li>• Hormonal dysregulation from hypothalamic–pituitary–ovarian axis (HPOA) disruption: stress, weight change, excessive exercise or rapid BMI shifts alter GnRH pulsatility, causing low or erratic LH/FSH secretion and reduced ovarian estrogen/progesterone production; this leads to anovulation, oligomenorrhea or amenorrhea commonly seen in young students.</li> <li>• Ovarian/endocrine pathophysiology (PCOS and prostaglandin-driven dysmenorrhea): hyperandrogenism and insulin resistance promote ovarian follicle arrest and chronic anovulation, while increased endometrial prostaglandin synthesis causes painful, heavy menses (dysmenorrhea) and worsens functional menstrual problems.</li> </ul>	<p>[71]</p>
<p>The quantity or quality of carbohydrates in one's diet is linked to ovulatory infertility.</p>	<p>Married and premenopausal women=18555</p>	<p>The quantity and quality of carbohydrates in the diet may play a significant role in influencing ovulation and fertility among healthy women.</p>	<ul style="list-style-type: none"> <li>• Insulin Signaling and Hyperandrogenism: High-quantity or low-quality (high glycemic index) carbohydrates cause rapid spikes in blood glucose, triggering excess insulin secretion. Chronically high insulin levels hyper-stimulate the ovaries' theca cells, increasing the production of androgens (like testosterone) and decreasing sex hormone-binding globulin (SHBG). This localized hyperandrogenism disrupts normal follicular development, leading to ovulatory dysfunction.</li> <li>• AMPK Pathway and Oocyte Quality: High carbohydrate intake alters cellular energy sensing. When glucose is excessive, the adenosine monophosphate-activated protein kinase (AMPK) pathway—a key regulator of cellular energy homeostasis—is suppressed. This downregulation impairs mitochondrial function and increases reactive oxygen species (ROS) in oocytes, compromising spindle formation and chromosome segregation during meiosis, which ultimately reduces egg quality and fertility.</li> </ul>	<p>[72]</p>
<p>Nutritional geometry methods applied to <i>Drosophila</i> lines that vary solely in their mitochondrial DNA (mtDNA), with the objective of determining whether there exists nutrient-dependent mitochondrial genetic variation affecting male reproduction.</p>	<p><i>Drosophila melanogaster</i></p>	<p>The interaction between mitochondrial DNA and dietary habits in relation to fitness indicates that mtDNA is involved in the regulation of fitness that is dependent on diet.</p>	<ul style="list-style-type: none"> <li>• Mitonuclear Incompatibility and Nutrient Sensing: Different mitochondrial DNA variants (mitotypes) alter the structure of oxidative phosphorylation complexes, changing how efficiently cells process macronutrients. When a specific mitotype mismatched with a diet tries to signal metabolic stress, it alters the activation of core nutrient-sensing pathways like mechanistic target of rapamycin (mTOR) and AMPK, directly impacting organismal fitness and lifespan based on whether the diet is high-protein or high-carbohydrate.</li> <li>• Diet-Dependent ROS Production and Retrograde Signaling: Dietary nutrients serve as the substrates for the mitochondrial electron transport chain, which is partially encoded by mtDNA. Specific diet-mitotype combinations cause a mismatch in electron flow, leading to altered levels of ROS; these ROS molecules act as retrograde signals to the nucleus, shifting gene expression related to stress tolerance and metabolic adaptation.</li> </ul>	<p>[72]</p>



<p>The fertility of couples undergoing treatment with a daily tablet containing a patented blend of vitex agnus-castus (vitex) extract, lepidium meyenii (maca) extract, and active folate, either alone or in conjunction with a gel capsule comprising vitamins, minerals, oligo-elements, as well as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) omega 3 fatty acids.</p>	<p>Clinical trial (n=189)</p>	<p>The patented formulation, which includes a mixture of vitex, maca, and active folate, helps to regulate the menstrual cycle, promotes ovulation, and enhances the chances of conception.</p>	<ul style="list-style-type: none"> <li>• Mitonuclear Co-adaptation and OXPHOS Efficiency: Mitochondrial DNA encodes core subunits of the oxidative phosphorylation (OXPHOS) pathway, while the remaining subunits are encoded by nuclear DNA. Dietary macronutrients (like fats versus carbohydrates) alter the cellular metabolic demand, requiring precise coordination between these two genomes. Specific mtDNA variants (mitotypes) interact differently with nuclear DNA under distinct diets, shifting the efficiency of adenosine triphosphate production versus ROS generation, which ultimately dictates an organism's physical fitness and metabolic adaptation.</li> <li>• Nutrient-Sensing Epigenetic and Retrograde Signaling: Dietary habits influence the availability of metabolic intermediates [such as nicotinamide adenine dinucleotide (NAD<sup>+</sup>), acetyl-CoA, and alpha-ketoglutarate] that serve as substrates for epigenetic modifications. When a specific mtDNA variant experiences metabolic stress from a mismatched diet, it triggers mitochondrial retrograde signaling to the nucleus (via or AMPK activation). This alters nuclear gene expression and mitochondrial biogenesis, directly impacting muscle endurance, energy expenditure, and overall fitness traits.</li> </ul>
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[72]

GnRH= gonadotropin-releasing hormone, FSH/LH=follicle-stimulating hormone/luteinizing hormone



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**Figure 2:** Schematic representation of the effect of sedentary lifestyle, junk food on molecular pathways linking PCOS, endometriosis, and infertility. Lifestyle and metabolic risk factors: sedentary lifestyle, high intake of junk food, and vitamin D deficiency are shown as the determinants. These factors promote systemic metabolic dysfunction, including insulin resistance and obesity. The metabolic consequences drive nutrient-sensing and stress-response nodes of altered AMPK activity and altered FOXO transcription factor signaling. The altered AMPK/FOXO pathways lead to PCOS manifestations and persistence of endometriosis. PCOS=polycystic ovary syndrome, AMPK = adenosine monophosphate-activated protein kinase, FOXO=Forkhead box transcription factors. ↓= decrease, ↑=increase, +=stimulation.

metabolic dysfunction, chronic inflammation, and female infertility [79–82]. Frequent consumption of junk food, fast food, and ultra-processed diets rich in saturated fats, refined sugars, artificial additives, and low-fiber content profoundly alters gut microbial diversity and composition, thereby disrupting intestinal metabolic homeostasis [79–82]. Such dietary patterns reduce beneficial microbial populations involved in short-chain fatty acid (SCFA) production while simultaneously promoting the proliferation of pro-inflammatory gram-negative bacteria. This microbial imbalance compromises intestinal barrier integrity by disrupting tight junction proteins, leading to increased intestinal permeability

or “leaky gut” phenomenon [79–82]. Enhanced intestinal permeability facilitates translocation of lipopolysaccharides and other endotoxins into systemic circulation, resulting in metabolic endotoxemia and activation of chronic low-grade inflammatory pathways [79–82]. LPS-mediated activation of toll-like receptor-4 (TLR4) signalling stimulates nuclear factor kappa B (NF-κB)-dependent inflammatory cascades, increasing production of pro-inflammatory cytokines such as TNF-α, IL-6, and interleukin-1β (IL-1β) [79–82]. These inflammatory mediators interfere with insulin receptor signalling pathways, aggravating insulin resistance and hyperinsulinemia, which are central pathogenic mechanisms



underlying PCOS-associated infertility and ovulatory dysfunction [79–82]. Hyperinsulinemia further stimulates ovarian theca cells to enhance androgen biosynthesis while suppressing hepatic SHBG synthesis, thereby increasing free androgen concentrations and promoting follicular arrest and chronic anovulation.

Gut dysbiosis additionally affects reproductive endocrinology through modulation of estrogen metabolism and enterohepatic circulation. Altered microbial  $\beta$ -glucuronidase activity influences estrogen deconjugation and reabsorption, thereby disrupting circulating estrogen levels and hormonal homeostasis essential for folliculogenesis, ovulation, and endometrial receptivity [79–82]. Disturbed gut microbial composition may also impair synthesis of essential metabolites involved in neurotransmitter regulation, including serotonin, dopamine, and gamma-aminobutyric acid (GABA), thereby indirectly influencing HPOA regulation and GnRH pulsatility [79–82]. At the ovarian level, chronic systemic inflammation and oxidative stress associated with dysbiosis compromise follicular microenvironment integrity and oocyte competence. Increased ROS generation impairs mitochondrial function within ovarian cells, reducing ATP production required for oocyte maturation and embryonic development [79–82]. Inflammatory cytokines additionally disrupt granulosa cell steroidogenesis and follicular signalling pathways, thereby impairing ovulation and implantation potential. Dysbiosis-associated metabolic disturbances also alter adipokine secretion, particularly leptin and adiponectin signalling, further aggravating endocrine imbalance and reproductive dysfunction. Another critical aspect involves the role of endocrine-disrupting chemicals, food preservatives, emulsifiers, artificial sweeteners, and trans fats commonly present in ultra-processed foods [79–82]. These compounds may directly interfere with hormone receptor signalling, steroidogenic enzyme activity, and epigenetic regulation of reproductive genes. Experimental studies suggest that such dietary components influence DNA methylation, histone modification, and microRNA expression associated with metabolic regulation, inflammation, and ovarian physiology [79–82]. Furthermore, disturbed circadian eating behaviour frequently associated with fast food consumption disrupts hormonal synchronization involving LH, cortisol, and melatonin secretion, thereby destabilizing menstrual cyclicity and reproductive endocrine regulation [69,70,72].

Collectively, current molecular and experimental evidence strongly supports gut dysbiosis as a central mediator linking unhealthy dietary patterns with infertility, PCOS progression, chronic inflammation, oxidative stress, and endocrine dysfunction. These findings highlight the potential therapeutic significance of microbiota-targeted nutritional interventions, dietary modification, and restoration of intestinal metabolic homeostasis in improving female reproductive health and fertility outcomes [79–82].

### Experimental and clinical evidence linking unhealthy diets with infertility

Experimental, epidemiological, and clinical studies consistently demonstrate a strong association between unhealthy dietary patterns and adverse reproductive outcomes

[12,18,21–23,28,66–72]. Observational studies indicate that women with frequent consumption of junk food and fast food exhibit higher prevalence of menstrual irregularities, dysmenorrhea, oligomenorrhea, premenstrual syndrome, obesity, and PCOS-associated infertility [12,18,21–23,28]. Diets rich in refined carbohydrates and trans fats have also been associated with reduced ovulatory fertility and impaired endocrine balance [87,88]. Clinical evidence further suggests that regular intake of ultra-processed foods increases the risk of insulin resistance, dyslipidemia, obesity, and metabolic syndrome, all of which adversely affect ovarian physiology and reproductive competence [83,84]. Elevated triglycerides, reduced high-density lipoprotein (HDL) levels, and ectopic lipid accumulation impair endothelial function and ovarian blood flow, thereby negatively influencing follicular development, fertilization, and implantation processes [34,35]. Studies additionally report that women consuming fast food more than once daily experience significantly higher infertility risk and poorer reproductive outcomes compared with individuals following balanced dietary practices [66–72].

Epidemiological studies in adolescents and young women indicate that excessive junk food consumption may contribute to earlier onset of menarche, which is associated with long-term endocrine and metabolic consequences including increased risk of PCOS and infertility later in life [12,18,21–23,28]. Experimental studies also reveal that diets high in saturated fats and refined sugars alter prostaglandin metabolism, particularly increasing pro-inflammatory prostaglandin  $F_{2\alpha}$  (PGF $_{2\alpha}$ ), thereby contributing to uterine hypercontractility, dysmenorrhea, and menstrual disturbances [69,85]. Importantly, several interventional and nutritional studies demonstrate that dietary modification can improve reproductive outcomes by restoring metabolic and endocrine homeostasis [66–72]. Balanced diets enriched with antioxidants, fiber, omega-3 fatty acids, vitamins, and micronutrients improve insulin sensitivity, reduce oxidative stress, and support ovarian function [86,87]. Dietary restriction and nutritional optimization further activate protective metabolic pathways involving FOXO and AMPK signalling, thereby improving mitochondrial function, reducing inflammatory burden, and preserving ovarian reserve [75,76,88].

However, variability in study design, dietary assessment methods, and population characteristics limits direct comparison across studies [86,87]. Despite these limitations, current evidence strongly supports the concept that junk food and ultra-processed dietary patterns represent significant modifiable risk factors for female reproductive dysfunction. Collectively, the available experimental and clinical findings reinforce the importance of dietary regulation, nutritional awareness, and lifestyle-based interventions as central preventive and therapeutic strategies for improving fertility outcomes and reproductive health in women [12,18,21–23,28,86,87].

### PCOS: A nexus of lifestyle–genetic interaction

The multidimensional metabolic, endocrine, inflammatory, and reproductive disturbances associated with PCOS strongly



support the recently proposed nomenclature shift toward “Polyendocrine Metabolic Ovarian Syndrome (PMOS),” which more accurately reflects the systemic nature of the disorder rather than limiting it to ovarian morphology alone. The findings discussed in this review demonstrate that insulin resistance, chronic inflammation, vitamin D deficiency, adipokine imbalance, and lifestyle-associated metabolic dysfunction collectively contribute to reproductive impairment, emphasizing the broader metabolic complexity underlying the syndrome. Furthermore, the beneficial impact of healthy dietary practices and regular physical activity on endocrine, metabolic, and reproductive homeostasis reinforces the concept that PMOS is fundamentally a multisystem metabolic-reproductive disorder influenced by modifiable lifestyle factors. Exercise-induced activation of AMPK promotes fatty acid oxidation, improves glucose uptake through enhanced GLUT4 expression, and restores metabolic balance. These changes contribute to normalization of ovarian steroidogenesis, improved follicular maturation, and restoration of ovulatory cycles. Exercise additionally stimulates eNOS activity, improving vascular function and blood circulation to reproductive tissues. Enhanced ovarian perfusion supports follicular development and endometrial receptivity, thereby improving implantation potential and pregnancy outcomes. At the molecular level, physical activity promotes mitochondrial biogenesis through activation of PGC-1 $\alpha$ , enhancing oxidative metabolism and reducing ROS accumulation. Exercise also suppresses inflammatory pathways by reducing TNF- $\alpha$  and IL-6 levels while increasing anti-inflammatory mediators. Improved insulin receptor phosphorylation and activation of PI3K/Akt pathways further restore insulin signalling and ovarian function. An equally important aspect highlighted in this review is the neuroendocrine and psychological benefit of exercise. Physical activity modulates HPA axis activity, reduces cortisol levels, improves serotonergic and dopaminergic signalling, and enhances release of endorphins and BDNF. These neuropsychological improvements reduce infertility-associated stress and indirectly restore reproductive endocrine balance [18,19,21-29,38-65].

Evidence summarized in this review consistently indicates that moderate-intensity exercise improves ovulation rates, menstrual regularity, hormonal balance, and pregnancy outcomes, particularly in overweight and PCOS populations. However, the review also acknowledges that excessive exercise and severe caloric restriction may induce hypothalamic suppression and anovulation, emphasizing the need for balanced and individualized physical activity recommendations. Healthy dietary habits similarly exert protective effects on reproductive physiology by restoring metabolic and endocrine homeostasis. Nutrient-dense and balanced diets improve insulin sensitivity, reduce inflammation, and provide essential micronutrients required for oocyte maturation, hormonal synthesis, antioxidant defense, and reproductive tissue integrity. Dietary interventions modulate nutrient-sensing pathways including FOXO, mTOR, and AMPK, thereby promoting mitochondrial function, cellular repair, oxidative stress resistance, and preservation of ovarian reserve. Caloric optimization and balanced nutrition improve metabolic signalling and create a favourable endocrine environment for ovulation, fertilization, and implantation. The review further emphasizes that combined

lifestyle interventions involving structured exercise, healthy dietary modification, micronutrient optimization, and weight regulation yield superior reproductive outcomes compared with isolated interventions. Such integrated approaches improve insulin sensitivity, reduce hyperandrogenism, normalize menstrual cyclicity, and enhance fertility potential [56-65,73-78,88].

## Genetic roots of infertility

### Chromosomal abnormalities

Chromosomal abnormalities, including monosomy X and structural rearrangements, play a critical role in female infertility. These defects lead to premature depletion of primordial oocytes and impaired ovarian development. Such abnormalities often result in primary ovarian insufficiency and a reduced reproductive lifespan [89,90]. At a deeper level, chromosomal anomalies disrupt meiotic pairing and segregation, leading to genomic instability and increased oocyte apoptosis during fetal development. In conditions such as Turner syndrome (45,X), haploinsufficiency of X-linked genes essential for ovarian maintenance accelerates follicular atresia [89,90]. Structural abnormalities, including translocations and deletions, may impair genes involved in DNA repair, synapsis, and recombination, further compromising oocyte viability. Additionally, chromosomal mosaicism can result in variable phenotypic expression, complicating diagnosis and prognosis. These genetic disruptions ultimately reduce the ovarian reserve and impair reproductive competence at both developmental and functional levels [89,90].

### X-linked gene dysregulation

Several X-linked genes are essential for normal ovarian function and reproductive development. Mutations or dysregulation of genes such as methyl-CpG binding protein 2 (*MECP2*) and filamin A, alpha (*FLNA*) can disrupt cellular processes, leading to infertility. These genetic alterations highlight the importance of genomic integrity in maintaining reproductive health [91,92]. Expanding further, X-linked genes play crucial roles in folliculogenesis, steroidogenesis, and cellular signalling pathways [91,92]. Dysregulation of genes involved in chromatin remodelling, transcriptional control, and cytoskeletal organization affects granulosa cell function and oocyte maturation. For instance, *MECP2* influences epigenetic regulation through DNA methylation, while *FLNA* is involved in cytoskeletal integrity and signal transduction. Abnormal XCI patterns can also lead to skewed gene expression, further exacerbating ovarian dysfunction. Emerging evidence suggests that mutations in additional X-linked genes, such as bone morphogenetic protein 15 (*BMP15*) and fragile X messenger ribonucleoprotein 1 (*FMR1*) permutations contribute to ovarian insufficiency, reinforcing the role of gene dosage and epigenetic regulation in reproductive biology [106-109] [91-94].

### Germ cell depletion mechanisms

Accelerated loss of germ cells is a key factor in infertility and is often associated with defective signaling between oocytes and surrounding granulosa cells. Impaired cellular communication



leads to follicular atresia and reduced ovarian reserve. Understanding these mechanisms is essential for developing targeted therapeutic interventions [95,96]. Mechanistically, germ cell depletion is driven by apoptotic pathways, oxidative stress, and disrupted intraovarian signalling networks. Key signalling pathways such as PI3K-Akt, transforming growth factor- $\beta$  (TGF- $\beta$ ), and proto-oncogene, *KIT* ligand pathways regulate follicular survival and activation; their dysregulation leads to premature follicle activation or atresia [95,96]. Mitochondrial dysfunction within oocytes further exacerbates cellular damage by increasing ROSs production and reducing ATP availability [95,96]. Additionally, impaired gap junction communication between oocytes and granulosa cells disrupts nutrient and signal exchange, compromising follicular development. Environmental stressors and genetic predispositions together accelerate depletion of the follicular pool, ultimately reducing reproductive lifespan [95,96].

### Effects of vitamin D deficiency, insufficiency, and VDR polymorphisms on female reproductive health

Beyond its classical role in calcium homeostasis, vitamin D functions as a pleiotropic secosteroid hormone regulating multiple reproductive, metabolic, inflammatory, and cellular signalling pathways critical for ovarian physiology [18,19,21-25]. The biologically active form of vitamin D, 1,25-dihydroxyvitamin D<sub>3</sub> [1,25(OH)<sub>2</sub>D<sub>3</sub>], exerts its genomic effects through binding to the VDR, a ligand-activated nuclear transcription factor expressed in ovarian granulosa cells, theca cells, endometrial tissue, placenta, pituitary gland, and hypothalamic regions involved in reproductive regulation [18,19,21-25]. Following ligand binding, the VDR heterodimerizes with retinoid X receptor (RXR) and interacts with vitamin D response elements (VDREs) within promoter regions of target genes, thereby modulating transcriptional activity associated with steroidogenesis, folliculogenesis, insulin signalling, inflammation, and cellular differentiation. The cumulative molecular disturbances associated with VDD, vitamin D insufficiency (VDI), and VDR polymorphisms exert profound effects on female reproductive physiology by disrupting ovarian, metabolic, immunological, mitochondrial, and gut-microbiota-associated pathways [18,19,21-28,79-82]. At the ovarian level, impaired vitamin D signalling compromises follicular recruitment, granulosa cell proliferation, oocyte maturation, and steroid hormone synthesis, thereby increasing the risk of chronic anovulation, follicular arrest, diminished ovarian reserve, and infertility progression [18,19,21-28]. Altered regulation of CYP19A1-mediated aromatase activity, AMH signalling, and FSH receptor (FSHR) responsiveness further destabilizes estrogen-androgen balance, contributing to hyperandrogenism and PCOS/PMOS-associated reproductive dysfunction [19,21-25]. VDD additionally aggravates insulin resistance, adipokine imbalance, obesity, and chronic inflammatory activation, thereby creating a hostile endocrine milieu unfavourable for ovulation, fertilization, implantation, and embryonic development [18,19,21-28]. Reduced vitamin D-mediated activation of PI3K/Akt signaling impairs insulin receptor phosphorylation and glucose metabolism, resulting

in hyperinsulinemia-driven ovarian androgen excess [21-25]. Simultaneously, oxidative stress and mitochondrial dysfunction associated with impaired vitamin D signalling reduce ATP generation required for spindle formation, chromosomal stability, and oocyte competence [21-25]. Increased ROS accumulation further promotes granulosa cell apoptosis, follicular atresia, and premature ovarian aging.

Emerging evidence now strongly suggests that vitamin D also functions as an important regulator of gut microbiota composition and intestinal immune homeostasis, thereby linking VDD with gut dysbiosis-associated infertility [79-82]. Vitamin D signalling through VDR regulates intestinal epithelial barrier integrity, tight junction protein expression, mucosal immunity, and microbial diversity. Deficiency states impair gut barrier function, resulting in increased intestinal permeability or "leaky gut," which facilitates translocation of lipopolysaccharides and endotoxins into systemic circulation [79-82]. This metabolic endotoxemia activates TLR4 and NF- $\kappa$ B-mediated inflammatory pathways, increasing circulating pro-inflammatory cytokines such as TNF- $\alpha$ , IL-6, and IL-1 $\beta$  [79-82]. Chronic systemic inflammation further worsens insulin resistance, oxidative stress, and ovarian steroidogenic dysfunction, thereby aggravating infertility and PCOS/PMOS severity. VDD-associated gut dysbiosis may additionally influence reproductive endocrinology through altered microbial estrogen metabolism and enterohepatic circulation. Disruption of gut microbial  $\beta$ -glucuronidase activity affects estrogen deconjugation and reabsorption, thereby disturbing circulating estrogen levels essential for folliculogenesis, ovulation, and endometrial receptivity [79-82]. Altered gut microbial composition also affects synthesis of neurotransmitter precursors and SCFAs, which regulate HPOA signalling, GnRH pulsatility, and neuroendocrine homeostasis [79-82]. Consequently, gut dysbiosis associated with VDD may indirectly impair ovulatory cyclicality, menstrual regulation, and implantation potential.

At the endometrial and implantation level, impaired vitamin D signalling may disrupt decidualisation, angiogenesis, immune tolerance, and cytokine-mediated uterine receptivity [18,19,21-25]. Reduced VDR-mediated transcriptional activity affects genes involved in placental development and embryo implantation, potentially increasing the risk of implantation failure, recurrent pregnancy loss, and adverse reproductive outcomes. Furthermore, VDR polymorphisms such as FokI and BsmI may modify intestinal VDR expression, microbial interaction, inflammatory responsiveness, and systemic vitamin D bioavailability, thereby influencing individual susceptibility to metabolic and reproductive dysfunction [21-25].

Collectively, current molecular evidence suggests that vitamin D deficiency, VDR polymorphisms, oxidative stress, mitochondrial dysfunction, and gut dysbiosis form an interconnected pathogenic network influencing ovarian physiology, endocrine balance, immune regulation, metabolic homeostasis, and reproductive competence [18,19,21-28,79-82]. These findings strongly reinforce the importance of gene-



nutrient–microbiome interactions in female infertility and highlight the therapeutic potential of vitamin D optimization, microbiota-targeted nutritional interventions, and metabolic regulation in improving reproductive health outcomes.

### Future perspective: From association to Precision-Based reproductive intervention

The evidence synthesized throughout this review strongly establishes female infertility as a systems-level metabolic–endocrine disorder arising from continuous interactions among genetic susceptibility, endocrine imbalance, metabolic dysfunction, micronutrient deficiency, environmental exposure, and lifestyle behavior. Among the major contributors, PCOS/PMOS emerges as one of the most significant infertility-associated conditions characterized by insulin resistance, hyperandrogenism, chronic inflammation, oxidative stress, mitochondrial dysfunction, and impaired folliculogenesis [12,18–29,34,35,73–78,83,84,86,87]. The interconnected influence of junk food consumption, sedentary lifestyle, gut dysbiosis, and vitamin D deficiency further highlights that reproductive dysfunction cannot be interpreted solely within the boundaries of ovarian pathology, but rather as a multisystem metabolic disorder profoundly shaped by modifiable environmental and nutritional factors. The future of reproductive medicine must therefore advance beyond associative observations toward mechanistically driven, precision-based, and translational frameworks. Large-scale longitudinal and multi-omics studies integrating genomics, epigenomics, metabolomics, transcriptomics, and microbiome profiling are urgently required to decode the complex molecular networks linking lifestyle-associated metabolic dysfunction with infertility progression. Such approaches may facilitate identification of predictive biomarkers for early detection, risk stratification, disease progression, and individualized therapeutic targeting [12,18–29,34,35,73–78,83,84,86,87].

Future research should particularly prioritize gene–environment and gene–nutrient interaction models involving vitamin D signalling, VDR polymorphisms, insulin resistance pathways, oxidative stress regulators, inflammatory mediators, and nutrient-sensing networks such as AMPK, mTOR, FOXO, and PI3K/Akt pathways. These mechanistic insights will strengthen the development of nutrigenomics-based and lifestyle-oriented precision medicine strategies for infertility and PCOS/PMOS management. Equally important is the need for well-designed randomized controlled trials evaluating integrated lifestyle interventions combining structured physical activity, dietary optimization, micronutrient supplementation, circadian regulation, and behavioural therapy. Considering the marked heterogeneity across metabolic phenotypes, genetic backgrounds, and socio-cultural environments, future reproductive healthcare must increasingly adopt individualized and personalized intervention models rather than uniform therapeutic protocols [12,18–29,34,35,73–78,83,84,86,87].

Emerging technologies including artificial intelligence-driven predictive analytics, wearable metabolic monitoring systems, and digital reproductive health platforms should also be incorporated into fertility management to enable continuous

lifestyle surveillance and real-time therapeutic modulation. From a broader public health perspective, infertility should be recognized as a lifestyle-linked non-communicable disorder requiring preventive policy-level interventions emphasizing nutritional awareness, physical activity, environmental safety, early metabolic screening, and reproductive health education. Such integrative and preventive strategies may substantially reduce the growing global burden of infertility while improving long-term reproductive and metabolic health outcomes in women [43–51,38–42,52–65].

### Conclusion

Female infertility can no longer be viewed through a fragmented lens of isolated endocrine or structural abnormalities; rather, it must be recognized as a systems-level disorder governed by the dynamic interplay of genetic, molecular, metabolic, and lifestyle determinants. The present synthesis unequivocally establishes that sedentary behaviour and unhealthy dietary patterns are not peripheral influences but central drivers of reproductive dysfunction, operating through IR, chronic inflammation, oxidative stress, and endocrine disruption. These pathways converge on critical regulatory axes—including the HPOA, adipokine signalling, and nutrient-sensing networks—ultimately impairing ovulation, oocyte quality, and implantation potential. Importantly, the interaction between intrinsic factors such as chromosomal integrity, gene regulation, and ovarian reserve with extrinsic modulators like physical inactivity and nutrient imbalance defines the phenotypic expression and severity of infertility. Conditions such as PCOS exemplify this convergence, where metabolic dysregulation, micronutrient deficiencies (notably vitamin D), and genetic susceptibility collectively shape reproductive outcomes. Thus, infertility should be redefined not merely as a reproductive disorder but as a metabolic–endocrine continuum influenced by modifiable lifestyle behaviours. This paradigm mandates a decisive shift in both clinical and research approaches—from reactive treatment strategies to preventive, integrative, and systems-based interventions. Lifestyle optimization is not an adjunct but a primary therapeutic axis, capable of restoring physiological equilibrium and enhancing reproductive potential. The evidence presented herein compels clinicians, researchers, and public health systems to reposition lifestyle as a cornerstone in the management and prevention of female infertility.

In essence, the next frontier lies in transforming our understanding of infertility from a condition to be treated into a biological state to be predicted, prevented, and precisely modulated.

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