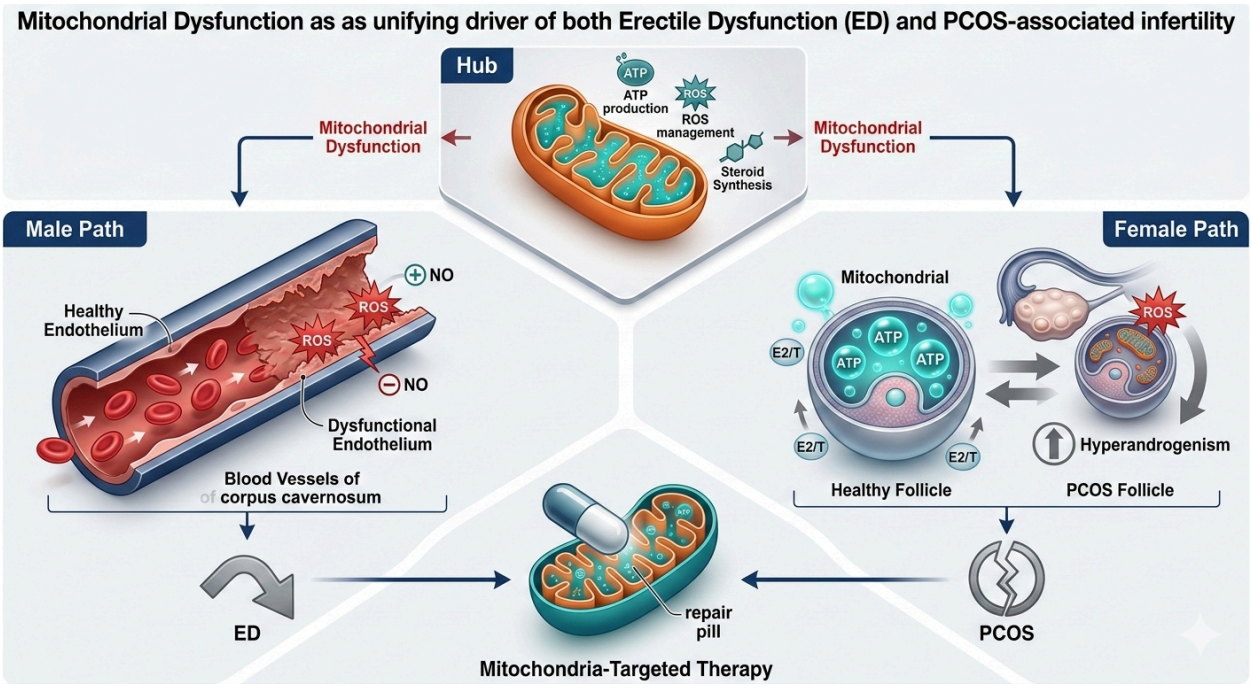
Mitochondrial Dysfunction: A responsible factor for the cause of PCOS in women, Erectile dysfunction in men and infertility in both.

Abstract:

Erectile dysfunction (ED) in men and polycystic ovary syndrome (PCOS) related infertility in women are increasingly prevalent conditions that extend beyond reproductive health, reflecting deeper systemic metabolic disturbances. While these disorders are traditionally studied independently, emerging evidence suggests a shared upstream driver: mitochondrial dysfunction. Mitochondria are essential for cellular energy production, redox balance, steroid hormone synthesis, and nitric oxide-mediated vascular signaling. Disruption of these functions can have profound consequences for both male and female reproductive physiology. In men, erectile function depends on intact endothelial signaling and nitric oxide bioavailability. Mitochondrial oxidative stress impairs vascular relaxation by promoting reactive oxygen species (ROS) accumulation and uncoupling of endothelial nitric oxide synthase, thereby reducing nitric oxide production and compromising cavernosal smooth muscle responsiveness. These changes are particularly evident in metabolic conditions such as obesity and diabetes, positioning ED as an early vascular manifestation of systemic mitochondrial injury. In women, ovarian function is highly dependent on mitochondrial integrity. Steroidogenesis begins within the mitochondria, and adequate ATP production is critical for follicular maturation and oocyte competence. In PCOS, mitochondrial abnormalities, including altered mtDNA copy number, increased oxidative stress, and impaired membrane potential disrupt granulosa cell metabolism and contribute to hyperandrogenism, anovulation, and reduced oocyte quality. This whitepaper proposes that mitochondrial dysfunction represents a unifying bioenergetic mechanism underlying both ED and PCOS-associated infertility. By reframing these conditions within a shared metabolic framework, we highlight opportunities for novel biomarkers and mitochondria-targeted therapeutic strategies aimed at restoring reproductive health through improved cellular energy resilience.



Introduction:

Infertility and sexual dysfunction are increasingly recognized not merely as isolated reproductive disorders but as early manifestations of systemic metabolic and vascular compromise. According to the World Health Organization, approximately 17.5% of the global adult population nearly one in six individuals experience infertility at some point in their lifetime. This growing burden reflects broader shifts in metabolic health, lifestyle patterns, and environmental exposures that increasingly affect individuals during their reproductive years. **(Okobi, 2021)**

Erectile dysfunction (ED) represents one of the most common forms of male sexual dysfunction. Data from the landmark Massachusetts Male Aging Study demonstrated that 52% of men aged 40-70 years reported some degree of erectile dysfunction, ranging from minimal to complete impairment. Furthermore, global projections estimate that the number of men affected by ED increased from 152 million in 1995 to a projected 322 million by 2025, driven largely by aging populations and the rising prevalence of diabetes, obesity, and cardiovascular disease.**(Yafi et al., 2016)**

Polycystic ovary syndrome (PCOS), the leading cause of anovulatory infertility, affects approximately 8-13% of women of reproductive age globally, depending on diagnostic criteria. In India, prevalence estimates vary widely, ranging from 5.8% using NIH criteria to as high as 19.6% under Rotterdam criteria, with pooled analyses suggesting an average prevalence of approximately 11.3%. Urbanization, dietary transitions, sedentary lifestyles, and insulin resistance are considered major contributors to this rising trend. **(Bharali et al., 2022)**

What is particularly striking is the shared metabolic landscape underlying both conditions. ED is strongly associated with diabetes, hypertension, and cardiovascular disease, while PCOS is

closely linked to insulin resistance, obesity, type 2 diabetes, and chronic low-grade inflammation. At the center of these metabolic disturbances lies mitochondrial dysfunction, a**(Rojas et al., 2014)**

Mitochondria regulate nitric oxide mediated endothelial function critical for penile erection and drive ovarian steroid hormone synthesis essential for ovulation and fertility. When mitochondrial bioenergetics decline and oxidative stress rises, vascular integrity in men and ovarian function in women are compromised. Thus, ED and PCOS may represent sex-specific clinical expressions of a shared bioenergetic pathology.**(Gómez del Val et al., 2025)**

This whitepaper explores mitochondrial dysfunction as a unifying mechanistic framework linking male erectile dysfunction and female PCOS-associated infertility, offering a systems-level perspective for clinicians and researchers seeking integrative therapeutic strategies.

Pathophysiology:

2.1 Erectile Dysfunction: A Mitochondrial-Vascular Disorder

Penile erection is a neurovascular event fundamentally dependent on endothelial integrity, nitric oxide (NO) signaling, and smooth muscle relaxation within the corpora cavernosa. Under physiological conditions, sexual stimulation activates parasympathetic pathways that stimulate endothelial nitric oxide synthase (eNOS), leading to nitric oxide release. NO diffuses into adjacent smooth muscle cells, activates guanylate cyclase, increases cyclic guanosine monophosphate (cGMP), and promotes vasodilation and increased penile blood flow.**(Burnett, 2006)**

Mitochondrial ROS and Nitric Oxide Impairment

Mitochondria are both generators and regulators of reactive oxygen species (ROS). Under metabolic stress such as hyperglycemia, obesity, or chronic inflammation, mitochondrial electron transport chain inefficiency leads to excessive superoxide production. Elevated ROS oxidizes tetrahydrobiopterin (BH4), a critical cofactor for endothelial nitric oxide synthase. This results in eNOS uncoupling, whereby the enzyme produces superoxide instead of nitric oxide, further amplifying oxidative stress and reducing NO bioavailability.**(Forrester et al., 2018)**

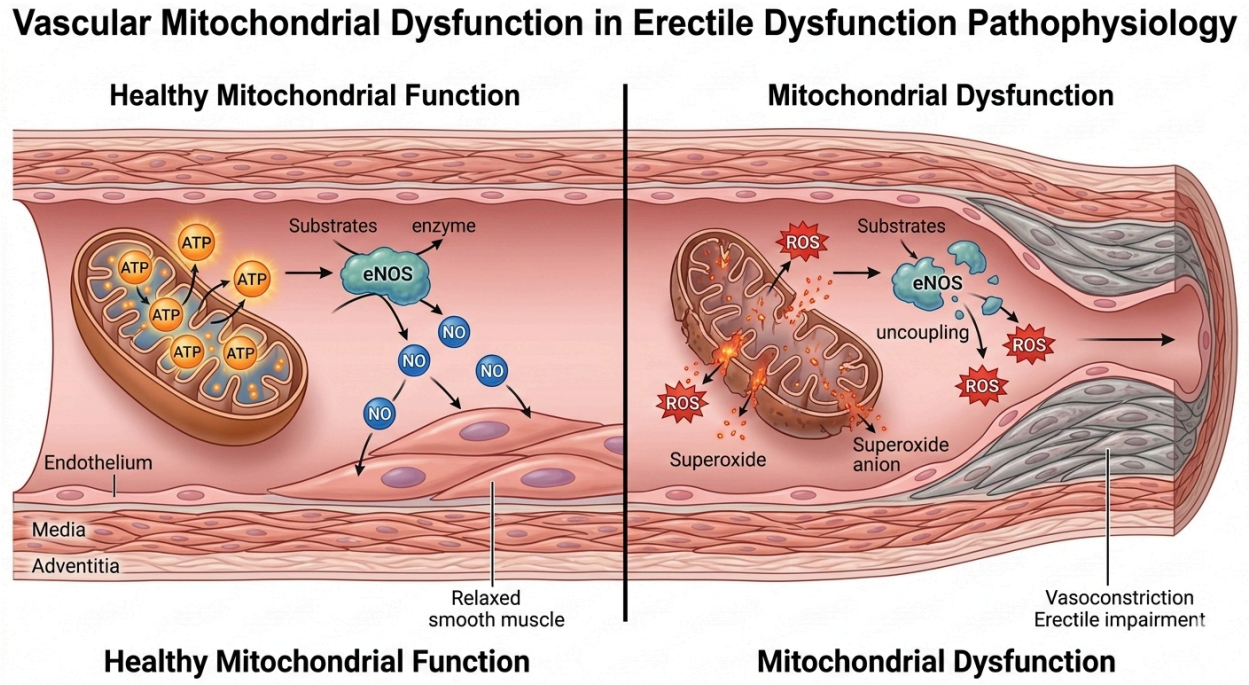
Reduced NO signaling directly compromises cavernosal smooth muscle relaxation, impairing erection. Importantly, mitochondrial oxidative stress precedes overt vascular structural damage, suggesting ED may be an early clinical marker of systemic mitochondrial dysfunction.

Bioenergetic Failure in Cavernosal Tissue

Penile tissue is metabolically active and requires adequate ATP for smooth muscle contraction-relaxation cycling. Mitochondrial dysfunction reduces oxidative phosphorylation

efficiency, leading to ATP depletion and impaired calcium handling in smooth muscle cells. Energy deficiency further predisposes to apoptosis of endothelial and smooth muscle cells, promoting fibrosis and loss of vascular elasticity.[1] **(Bhatti et al., 2017)**

Over time, chronic mitochondrial stress contributes to structural remodeling of penile vasculature, compounding functional impairment.



2.2 Metabolic Comorbidities and Mitochondrial Injury

ED rarely exists in isolation. It is strongly associated with:

- Type 2 diabetes mellitus

Insulin resistance, the hallmark of T2DM, further exacerbates mitochondrial dysfunction by disrupting substrate utilization and promoting lipid accumulation within non-adipose tissues (lipotoxicity). Excess intracellular fatty acids impair mitochondrial β-oxidation, generate additional ROS, and activate inflammatory pathways such as NF-κB. In PCOS, insulin resistance stimulates hyperinsulinemia, which drives ovarian androgen overproduction, disrupting ovulatory cycles. Thus, T2DM is not merely a metabolic disorder but a systemic mitochondrial disease that directly impacts vascular, endocrine, and reproductive health.**(Sergi et al., 2019)**

- Obesity

Adipose tissue in obesity also functions as an active endocrine organ, secreting inflammatory cytokines such as TNF-α and IL-6, which directly inhibit mitochondrial respiration and

biogenesis. Chronic inflammation suppresses PGC-1α, a master regulator of mitochondrial biogenesis, thereby reducing mitochondrial density in skeletal muscle and reproductive tissues. The resulting metabolic inflexibility reinforces insulin resistance and hormonal imbalance. In PCOS, obesity amplifies hyperandrogenism and ovulatory dysfunction, while in men it reduces testosterone levels, both outcomes tightly linked to impaired mitochondrial steroidogenesis.**(Kirichenko et al., 2022)**

- Hypertension

At the cellular level, mitochondrial dysfunction in hypertension disrupts calcium handling and ATP-dependent vascular tone regulation. Reduced mitochondrial efficiency increases oxidative damage to mitochondrial DNA (mtDNA), perpetuating a cycle of impaired oxidative phosphorylation. In women with PCOS, hypertension often coexists with insulin resistance and metabolic syndrome, compounding vascular and ovarian dysfunction. Reduced uterine blood flow and endothelial dysfunction may negatively affect implantation and pregnancy outcomes, highlighting the systemic reproductive implications of hypertensive mitochondrial injury. **(Eirin et al., 2014)**

- Dyslipidemia

In ovarian physiology, excess circulating lipids accumulate within follicular fluid, altering the metabolic microenvironment of the developing oocyte. Lipotoxicity disrupts mitochondrial membrane potential, increases oxidative stress, and impairs meiotic spindle formation. Dyslipidemia therefore compromises both male vascular performance and female gamete quality. Clinically, dyslipidemia often coexists with insulin resistance and obesity, creating a cumulative mitochondrial burden that accelerates reproductive dysfunction. **(X. Zhang et al., 2025)**

- Cardiovascular disease

Beyond vascular implications, systemic CVD reflects widespread metabolic inflexibility and impaired mitochondrial ATP generation. Reduced cardiac output and endothelial dysfunction can diminish reproductive organ perfusion, potentially affecting testicular steroidogenesis and ovarian follicular development. The shared mitochondrial pathology between CVD, ED, and PCOS reinforces the concept that reproductive dysfunction is often an early clinical expression of systemic metabolic and mitochondrial decline rather than an isolated organ disorder.**(Stamerra et al., 2022)**

These conditions share a common denominator: impaired mitochondrial metabolism.

Hyperglycemia increases mitochondrial ROS through excess electron donor availability (NADH/FADH2 overload), activating inflammatory pathways such as NF-κB. Insulin resistance reduces mitochondrial biogenesis via suppression of AMPK and PGC-1α signaling, decreasing mitochondrial density and resilience. Lipotoxicity from elevated free fatty acids further disrupts mitochondrial membrane integrity and promotes apoptosis.**(Stamerra et al., 2022)** Thus, ED may represent a localized vascular manifestation of systemic metabolic mitochondrial stress.

2.3 PCOS: Ovarian Mitochondrial Dysfunction and Infertility

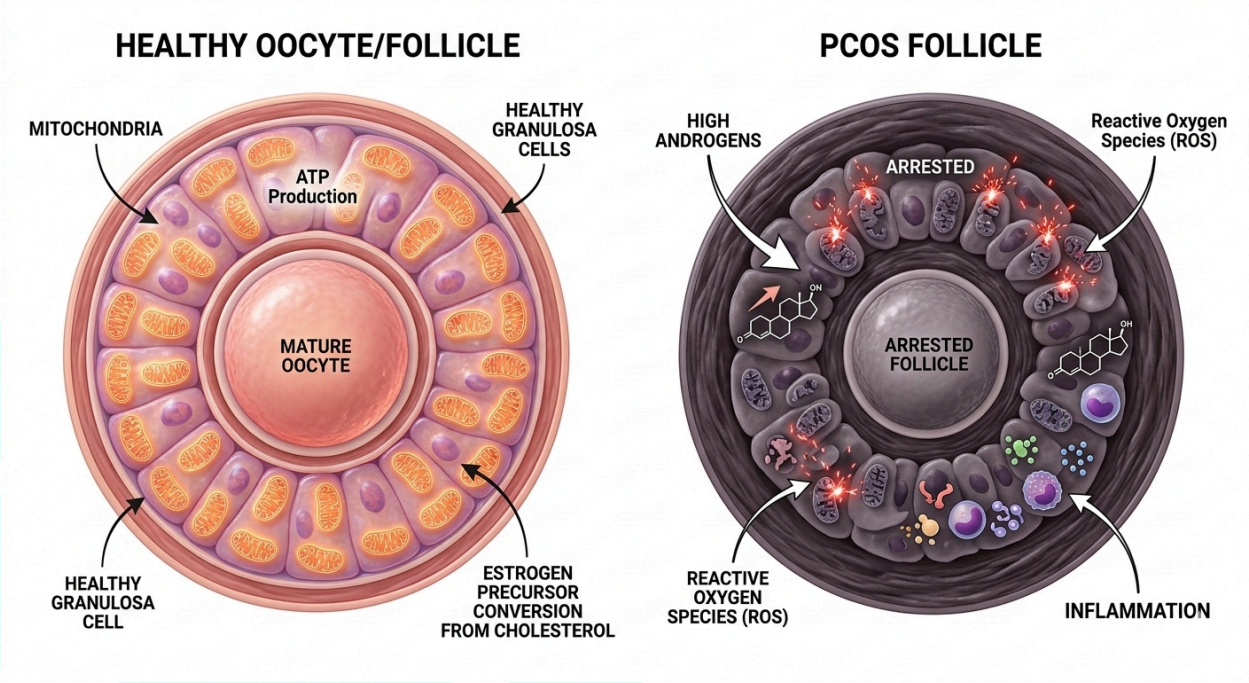
While ED primarily reflects vascular mitochondrial impairment, PCOS represents a mitochondrial-endocrine disorder centered in ovarian tissue.

Ovarian steroidogenesis begins within mitochondria, where cholesterol is transported and converted to pregnenolone, the precursor of progesterone, estrogen, and androgens. Adequate mitochondrial membrane potential and ATP production are essential for this process.

Mitochondrial Dysfunction and Hyperandrogenism

In PCOS, mitochondrial abnormalities, including reduced mtDNA copy number, altered mitochondrial membrane potential, and excessive ROS production, have been observed in granulosa cells. These changes impair normal steroidogenic enzyme activity, contributing to dysregulated androgen synthesis.**(Siemers et al., 2023)**

Excess ROS also activates inflammatory pathways within ovarian tissue, promoting granulosa cell apoptosis and follicular arrest. The resulting imbalance between follicle-stimulating hormone (FSH) and luteinizing hormone (LH) further exacerbates hyperandrogenism and anovulation.**(H. Liu et al., 2025)**



2.4 Insulin Resistance: The Shared Metabolic Bridge

Insulin resistance is a hallmark of PCOS and a major contributor to ED. Mitochondria play a central role in insulin sensitivity by regulating fatty acid oxidation and glucose metabolism.

Impaired mitochondrial β-oxidation leads to lipid accumulation within muscle and ovarian tissue, disrupting insulin signaling pathways. Hyperinsulinemia, in turn, stimulates ovarian theca cells to produce excess androgens, reinforcing the PCOS phenotype.**(Paneni, 2015)**

In men, insulin resistance accelerates endothelial dysfunction by increasing oxidative stress and decreasing NO bioavailability. Thus, mitochondrial dysfunction creates a vicious cycle linking metabolic disease to reproductive impairment in both sexes.**(Pastuszak, 2014)**

3. Current Standards of Care in Erectile Dysfunction, PCOS & Infertility

Modern management of erectile dysfunction (ED), polycystic ovary syndrome (PCOS), and infertility has evolved significantly over recent decades. Contemporary approaches are largely symptom-oriented and goal-directed, aimed at restoring sexual function, regulating hormonal imbalance, or achieving pregnancy. While these strategies have substantially improved clinical outcomes and quality of life, they primarily address downstream physiological disturbances rather than upstream cellular bioenergetics.**(Ahmed et al., 2021)**

Erectile Dysfunction

First-line therapy for ED consists of phosphodiesterase type 5 (PDE5) inhibitors such as Sildenafil and Tadalafil. These agents enhance nitric oxide-cGMP signaling by preventing cGMP degradation, thereby promoting cavernosal smooth muscle relaxation and improved penile blood flow. Clinical response rates are high in otherwise healthy men; however, efficacy declines significantly in patients with diabetes, metabolic syndrome, and advanced endothelial dysfunction.**(Rizk et al., 2017)**

In men with confirmed hypogonadism, testosterone replacement therapy may improve libido and partially enhance erectile function. Yet, hormonal correction alone does not reverse endothelial oxidative stress or mitochondrial impairment, both of which are central to vascular health.**(Vlaicu et al., 2026)**

Second-line therapies include intracavernosal injections of vasoactive agents such as Alprostadil, which directly induce smooth muscle relaxation independent of endogenous nitric oxide production. Mechanical devices and penile prosthesis implantation provide effective solutions in refractory cases but function as structural or compensatory interventions rather than

metabolic corrections. Thus, conventional ED management predominantly amplifies downstream vasodilatory signaling without restoring mitochondrial integrity within endothelial cells.**(Singh et al., 2023)**

PCOS management is tailored to clinical goals, cycle regulation, hyperandrogenism control, metabolic stabilization, or fertility induction. Combined oral contraceptives remain the cornerstone therapy for menstrual irregularity and androgen suppression. Anti-androgenic agents such as spironolactone are frequently added for hirsutism management. These therapies effectively regulate symptoms but do not directly improve insulin resistance or oxidative stress within ovarian tissue.**(Foretz et al., 2023)**

For PCOS & metabolic dysfunction, metformin is widely prescribed. Metformin improves insulin sensitivity, reduces hepatic gluconeogenesis, and activates AMP-activated protein kinase (AMPK), indirectly influencing mitochondrial biogenesis pathways. Among conventional therapies, metformin uniquely intersects with mitochondrial metabolism, although its effects are partial and not universally restorative.**(Herman et al., 2023)**

For ovulation induction, letrozole is now considered first-line therapy due to superior live birth rates compared to clomiphene citrate. While effective at stimulating follicular maturation, ovulation induction agents do not directly address mitochondrial dysfunction within granulosa cells or systemic metabolic inflammation.

Infertility Management

When pharmacologic ovulation induction fails or when male factors contribute significantly, assisted reproductive technologies (ART), including in vitro fertilization (IVF), are employed. These technologies can achieve successful pregnancy outcomes even in the presence of significant endocrine or metabolic dysfunction. However, they operate by bypassing intrinsic biological impairments rather than correcting them.**(Dube, 2016)**

Oocyte competence, sperm motility, and embryo viability are all highly dependent on mitochondrial ATP production and redox balance. Conventional fertility interventions do not directly target these bioenergetic determinants.

Clinical Perspective

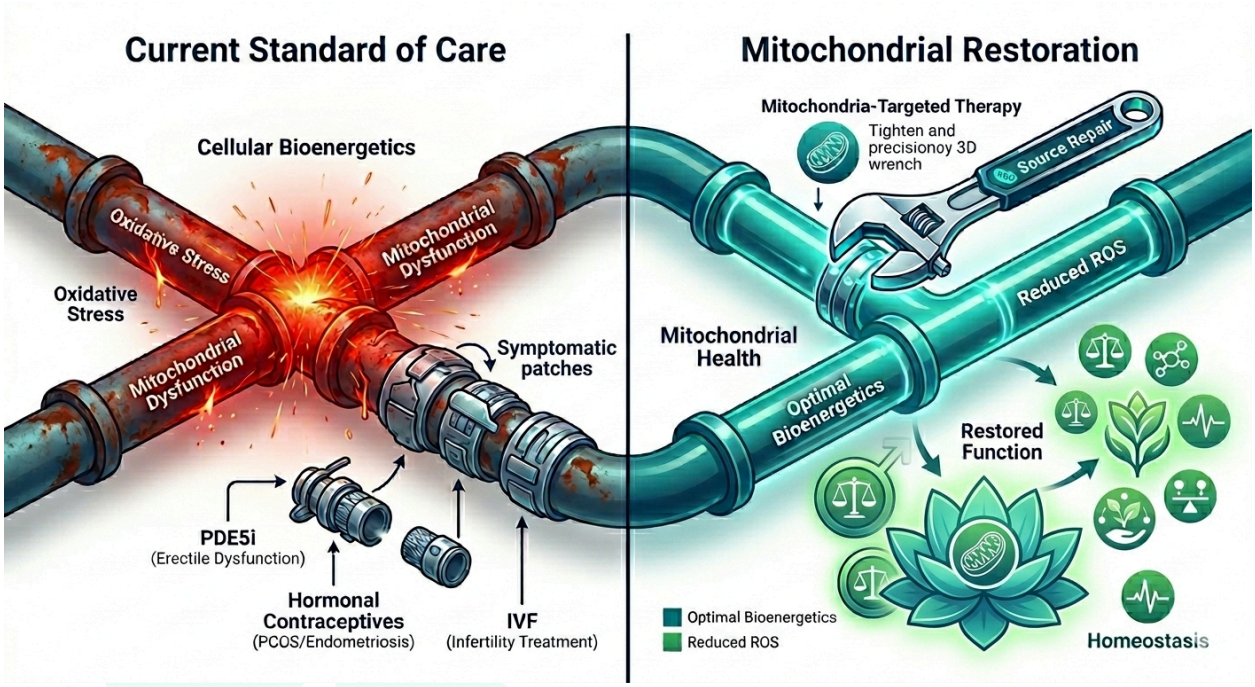
Conventional medicine has dramatically improved reproductive and sexual health outcomes. These therapies are evidence-based, clinically effective, and often life-changing. However, they primarily:

- Enhance vascular signaling
- Modulate hormonal output
- Induce ovulation
- Facilitate fertilization

They do not consistently restore:

- Mitochondrial oxidative balance
- Cellular ATP production
- Mitochondrial biogenesis
- Systemic metabolic resilience

Recognizing mitochondrial dysfunction as a shared upstream contributor to ED and PCOS does not undermine existing therapies. Rather, it creates an opportunity to complement symptom-directed treatment with metabolic and bioenergetic restoration strategies.



4. Functional Nutrition Approach

4.1 Root Causes: A Mitochondrial-Centered Framework

Erectile dysfunction (ED) and polycystic ovary syndrome (PCOS) are traditionally viewed through organ-specific lenses: vascular in men and endocrine-ovarian in women. However, mounting evidence suggests that both conditions share a deeper systemic origin rooted in mitochondrial dysfunction. From a functional medicine perspective, the clinical phenotype represents the final expression of long-standing disturbances in cellular energetics, redox biology, and metabolic signaling.**(Shaughnessy et al., 2014)**

Mitochondria are not merely energy generators; they regulate apoptosis, steroidogenesis, calcium signaling, nitric oxide balance, inflammation, and epigenetic expression. When mitochondrial resilience declines, tissues with high metabolic demand such as endothelial cells and ovarian follicles are disproportionately affected. Below are the principal upstream drivers of mitochondrial dysfunction relevant to ED, PCOS, and infertility.**(Tharayil & Shukla, 2025)**

4.1.1 Insulin Resistance and Metabolic Overload

Insulin resistance is a central pathological bridge linking ED and PCOS. At the mitochondrial level, chronic caloric excess, particularly refined carbohydrates and saturated fats leads to persistent nutrient oversupply. This generates an excess of reducing equivalents (NADH and $FADH_2$), overwhelming the electron transport chain (ETC). **(Napolitano et al., 2021)**

When electron flux exceeds mitochondrial capacity, electron leakage increases, forming superoxide radicals. Elevated reactive oxygen species (ROS) impair mitochondrial DNA (mtDNA), oxidize cardiolipin within the inner mitochondrial membrane, and reduce ATP synthesis efficiency. In men, insulin resistance impairs endothelial nitric oxide synthase (eNOS) activation, reducing nitric oxide bioavailability. In women, hyperinsulinemia directly stimulates ovarian theca cells to increase androgen production, reinforcing hyperandrogenism in PCOS.**(Abu Shelbayeh et al., 2023)**

Moreover, insulin resistance suppresses AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), both critical regulators of mitochondrial biogenesis. Reduced mitochondrial turnover further amplifies oxidative stress, creating a vicious metabolic cycle.**(Di Meo et al., 2016)**

4.1.2 Oxidative Stress and Redox Imbalance

Physiological levels of ROS serve signaling functions. However, chronic metabolic stress shifts redox balance toward oxidative injury. Mitochondrial ROS overproduction damages lipids, proteins, and nucleic acids, leading to impaired oxidative phosphorylation. In endothelial cells, ROS oxidize tetrahydrobiopterin (BH4), uncoupling eNOS and converting it from a nitric oxide producing enzyme into a superoxide-generating enzyme. This amplifies vascular dysfunction in ED.**(Yan et al., 2025)**

In ovarian granulosa cells, oxidative stress disrupts mitochondrial membrane potential and impairs steroidogenic enzyme activity. Follicular development becomes arrested, contributing to anovulation and reduced oocyte quality in PCOS. Furthermore, excessive ROS activates nuclear factor kappa B (NF-κB), promoting chronic low-grade inflammation, another shared feature of ED and PCOS.**(Janssen et al., 2019)**

4.1.3 Micronutrient Deficiency and Cofactor Insufficiency

Mitochondrial enzymes depend heavily on micronutrient cofactors, including magnesium, zinc, selenium, B vitamins, iron, and coenzyme Q10. Modern dietary patterns characterized by ultra-processed foods often lack these critical substrates.

Magnesium deficiency impairs ATP stabilization and insulin signaling. B vitamins (particularly B1, B2, B3, and B5) are essential for mitochondrial dehydrogenase reactions and electron transport chain function. Coenzyme Q10 facilitates electron transfer between Complexes I/II and III; depletion reduces ATP production and increases ROS generation. **(Cyr et al., 2020)**

In reproductive tissues, micronutrient insufficiency compromises steroidogenesis and gamete quality. In vascular tissue, it impairs endothelial repair and nitric oxide synthesis. Subclinical deficiencies may not present overt laboratory abnormalities yet significantly influence mitochondrial efficiency.**(Kim & Lee, 2025)**

4.1.4 Chronic Inflammation

Low-grade systemic inflammation, often driven by visceral adiposity and gut dysbiosis, directly impairs mitochondrial function. Pro-inflammatory cytokines such as TNF-α and IL-6 interfere with insulin signaling pathways and suppress mitochondrial biogenesis.

Inflammatory mediators increase nitric oxide scavenging in men and disrupt follicular microenvironments in women. Persistent inflammation also alters mitochondrial dynamics, reducing fusion processes necessary for mitochondrial repair. In PCOS, inflammatory markers are consistently elevated even in non-obese women, suggesting inflammation is intrinsic to the syndrome rather than solely secondary to adiposity.**(Engin, 2017)**

4.1.5 Lipotoxicity and Mitochondrial Membrane Injury

Elevated circulating free fatty acids contribute to ectopic lipid accumulation within muscle, liver, and ovarian tissue. In mitochondria, excess fatty acid intermediates disrupt membrane integrity and increase production of toxic lipid species such as ceramides.**(Lipke et al., 2022)**

In endothelial cells, lipotoxicity accelerates apoptosis and impairs vasodilatory responsiveness. In ovarian cells, it interferes with follicular maturation and steroid hormone synthesis. Cardiolipin oxidation, a hallmark of mitochondrial membrane damage, further compromises electron transport chain stability and ATP output.**(Reddam et al., 2022)**

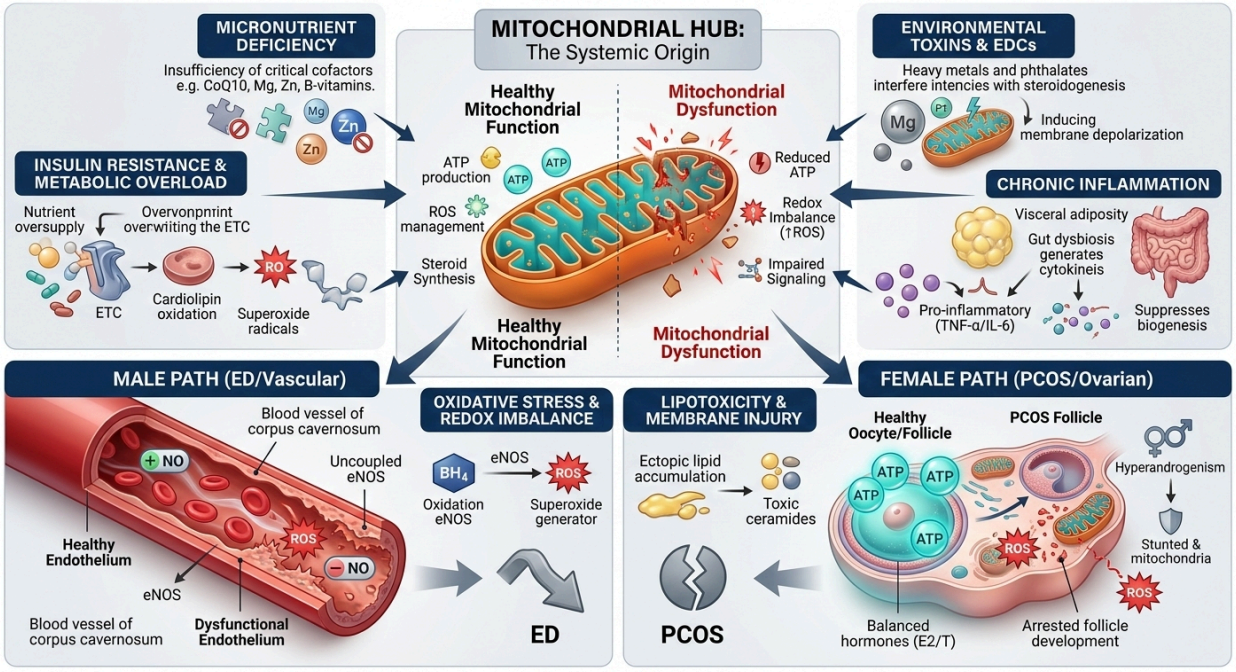
4.1.6 Environmental Toxins and Endocrine Disruptors

Exposure to environmental pollutants, heavy metals, and endocrine-disrupting chemicals has been increasingly implicated in reproductive dysfunction. Many of these agents impair mitochondrial respiration and increase oxidative stress.**(Lucas et al., 2022)**

Phthalates, bisphenols, and certain pesticides interfere with steroid hormone signaling and mitochondrial enzyme activity. Heavy metals such as cadmium and lead accumulate in reproductive tissues and induce mitochondrial swelling and membrane depolarization. Chronic low-dose exposure may silently erode mitochondrial capacity over years before clinical symptoms emerge.**(Bao et al., 2026)**

4.1.7 Circadian Disruption and Sleep Deprivation

Mitochondrial function is tightly regulated by circadian biology. Disrupted sleep patterns, shift work, and chronic light exposure alter melatonin secretion and impair mitochondrial antioxidant defenses. Melatonin itself is a potent mitochondrial antioxidant and regulator of electron transport chain efficiency. Reduced melatonin levels have been associated with both ED and PCOS. Sleep deprivation exacerbates insulin resistance, increases cortisol levels, and amplifies inflammatory signaling, further destabilizing mitochondrial homeostasis.**(Oteri et al., 2024)**



Dietary Interventions and Mitochondrial Function in ED, PCOS, and Infertility

Low-Glycemic/Anti-Inflammatory Diets

Healthy dietary patterns: Men adhering to a Mediterranean-style or DASH-like diet (rich in vegetables, fruits, legumes, olive oil, and fish) have a significantly lower risk of developing erectile dysfunction. These diets emphasize low glycemic load, high fiber and unsaturated fats, and are inherently anti-inflammatory and antioxidant-rich.

Oxidative stress reduction: Mediterranean-type diets provide polyphenols and micronutrients (e.g. extra-virgin olive oil phenolics, nuts, whole grains and removing inflammatory food) that reduce inflammation and oxidative stress. For example, olive oil polyphenols boost nitric oxide (NO) signaling and inhibit vascular inflammation, which protects penile endothelial function and improves blood flow.,**(Albardan et al., 2024)**

Glycemic control: Low-GI diets blunt postprandial glucose spikes, preventing "glucotoxicity" that otherwise generates mitochondrial ROS and triggers mitophagy. Stabilizing blood sugar helps maintain mitochondrial integrity. In insulin-resistant states (e.g. PCOS), diets like the DASH, Mediterranean or low-GI and high protein diet improve metabolic and reproductive features, lowering androgens and improving ovulation.**(Odetayo & Olayaki, 2023)**

Omega-3 Fatty Acids

Metabolic and inflammatory effects: In women with PCOS, supplementation with EPA/DHA (fish-oil omega-3s) consistently lowers serum triglycerides and has anti-inflammatory effects (reduced CRP, increased adiponectin).**(Odetayo & Olayaki, 2023)** Omega-3s also reduce androgens and improve insulin sensitivity, likely via enhanced fatty-acid oxidation and generation of pro-resolving mediators (resolvins). These effects support mitochondrial function by shifting energy metabolism toward fat oxidation and reducing chronic ROS.

Vascular and endocrine function: Omega-3s can directly enhance endothelial NO production. In animal models of erectile dysfunction, omega-3 intake restored NO/cGMP signaling and key steroidogenic enzyme activities. This suggests omega-3s improve both vascular (erectile) and hormonal function. Enhanced NO release and lowered vascular inflammation from omega-3s. **(Ardehjani et al., 2024)**

Polyphenols & Plant Antioxidants

Resveratrol (and others): Resveratrol supplementation in PCOS patients undergoing IVF markedly improved markers of mitochondrial biogenesis and function. A recent RCT showed resveratrol increased expression of PGC-1α and TFAM, elevated mitochondrial DNA copy number and ATP content in granulosa cells, and reduced follicular oxidative stress. Clinically this translated into higher oocyte maturation and embryo quality. In other words, resveratrol (a polyphenol) boosted mitochondrial biogenesis via SIRT1/PGC-1α pathways while lowering ROS, improving female gamete function.**(Zhu et al., 2024)**

Dietary antioxidants and ED: Higher dietary intake of antioxidants (vitamins A, C, E, selenium, zinc, carotenoids, etc.) strongly correlates with better erectile function. A large U.S. cohort study

found men in the highest tertile of a Composite Dietary Antioxidant Index (CDAI) had ~37% lower odds of ED. This likely reflects greater NO bioavailability and lower penile oxidative stress when consuming antioxidant-rich plant foods. Similarly, antioxidant polyphenols in fruits and vegetables protect sperm and oocyte integrity by neutralizing ROS. **(Ahmadi Asouri et al., 2024)**

Micronutrients (Mg, CoQ10, Se, Zn, B Vitamins)

Coenzyme Q10: CoQ10 is an essential electron carrier in the mitochondrial respiratory chain. In PCOS patients, CoQ10 supplementation improved insulin resistance and upregulated PPAR-γ expression. By supporting mitochondrial ATP synthesis and acting as an antioxidant, CoQ10 reduces metabolic stress. Meta-analyses confirm that CoQ10 lowers fasting glucose and lipids in PCOS, suggesting broader metabolic benefits via mitochondrial support. **(Rył et al., 2024a)**

Zinc: It is critical for testosterone synthesis and sperm health. It “sustains optimal testosterone levels” and preserves penile endothelial function. Deficiency impairs spermatogenesis, leading to reduced sperm count and motility, and causes low testosterone that contributes to ED. By supporting antioxidant enzymes and hormone biosynthesis, adequate Zn helps maintain mitochondrial integrity in reproductive tissues. **(Zhao et al., 2023)**

Selenium: Selenium (Se) is a cofactor for glutathione peroxidases. In PCOS trials, selenium supplementation significantly **increased total antioxidant capacity** in patients’ plasma. In other words, Se helped restore redox balance in the ovary/follicles. Although clinical improvements (e.g. BMI or insulin) were modest, enhanced antioxidant defenses suggest selenium may protect oocytes and endometrium from oxidative damage. Improved follicle quality from Se has been suggested for PCOS patients planning IVF. **(Rył et al., 2024b)**

Magnesium: It is required for nitric oxide synthase activity. One study notes that hypomagnesemia lowers NO levels, causing penile vasoconstriction and ED. Mg deficiency also impairs testosterone production. Thus, adequate magnesium supports endothelial/vascular function and steroidogenesis. By ensuring NO availability, Mg prevents mitochondrial overactivity and oxidative damage in vascular cells. **(Wu et al., 2025)**

B Vitamins: B vitamins are cofactors in mitochondrial metabolism. Thiamine (B1) is critical for carbohydrate oxidation; deficiency “induces mitochondrial dysfunction." A US study found that higher dietary thiamine intake was linked to markedly lower ED incidence, suggesting better energy metabolism protects endothelial cells.**(Tang et al., 2022)** Riboflavin (B2) activates AMPK and PGC-1α: in rats, B2 supplementation increased hepatic p-AMPK and PGC-1α, improving mitochondrial biogenesis and reducing oxidative stress. Thus, B-vitamins can enhance AMPK signaling and mitochondrial efficiency in reproductive tissues.**(Velissariou et al., 2025)**

Time-Restricted Feeding & Intermittent Fasting

Reproductive outcomes: Emerging clinical data in PCOS show that TRF/IF improves endocrine and fertility markers. In small trials, women with PCOS practicing 8-10-hour feeding windows had significantly more regular menstrual cycles and reduced testosterone, LH, and AMH, while SHBG and insulin sensitivity improved. These hormonal shifts (lower androgens, higher SHBG) favor ovulation and endometrial health.**(A. Zhang et al., 2024a)**

Cellular mechanisms: Fasting periods activate key energy-sensing pathways. IF is known to activate AMPK and SIRT1, which together induce PGC-1α and mitochondrial biogenesis. By upregulating AMPK/PGC-1α, TRF enhances mitochondrial number and function, boosting ATP production. Concurrently, IF/fasting reduces cellular ROS production and improves autophagy. In sum, fasting regimens improve metabolic flexibility and reduce oxidative stress in reproductive and vascular cells via AMPK/SIRT1/PGC-1α pathways.**(Porav-Hodade et al., 2025)**

Important markers to consider:

Erectile dysfunction:

Total and Free Testosterone (TT, FT): Low testosterone is a well-known cause of ED. Both total and especially free testosterone correlate strongly with erectile function as ED severity rises; TT and FT decline markedly. Testosterone stimulates libido and penile nitric-oxide production, so deficiency impairs erection. Clinical studies show TT and FT levels are significantly lower in men with ED, and free T (calculated via SHBG) often falls below normal. Thus measuring TT and calculating FT is routine in ED workups.
(C. Liu et al., 2023)

Insulin Resistance (HOMA-IR, fasting insulin/ fasting glucose): ED is strongly associated with metabolic syndrome and diabetes. Men with ED have markedly higher insulin resistance (e.g. elevated HOMA-IR or TyG index) than controls. Mechanistically, insulin resistance causes endothelial dysfunction (reduced nitric oxide, vascular stiffness) and decreases testosterone, all contributing to ED. A recent meta-analysis found significantly higher HOMA-IR in ED patients (standardized mean difference ≈0.6, $p<0.01$). Although HOMA-IR is mainly research-oriented, fasting glucose/insulin or lipid indices (LDL↑, HDL↓) are often checked in ED patients. This marker is **emerging** in ED evaluation as part of metabolic risk assessment. **(A. Zhang et al., 2024b)**

Inflammatory Markers (CRP, NLR, etc.): Chronic inflammation is implicated in ED pathophysiology. ED patients frequently have elevated systemic inflammatory indices (hs-CRP, IL-6, TNF-α, neutrophil–lymphocyte ratio, etc.). Inflammation impairs endothelial function and penile blood flow. For example, multiple studies show higher high-sensitivity CRP in men with ED. Large survey analyses (NHANES) report positive associations between ED and markers like NLR and systemic inflammation indices. These tests are not yet standard ED diagnostics, but they underscore the vascular/mitochondrial link: oxidative stress (from inflamed mitochondria) reduces NO availability in ED. **(Huffman et al., 2023)**

PCOS:

Anti-Müllerian Hormone (AMH): AMH is markedly elevated in PCOS (often ~3× higher than normal) because PCOS ovaries contain many small follicles. AMH reflects growing follicle count and correlates with polycystic ovarian morphology. Importantly, the 2023 international PCOS guidelines now allow elevated AMH (instead of ovarian ultrasound) as a diagnostic criterion in adults. Thus, serum AMH is increasingly used for PCOS screening. **(Verma, 2016)**

Serum Androgens (Total Testosterone, Free Androgen Index): Hyperandrogenemia is a core PCOS feature. About 80% of PCOS women have high circulating androgens. Total testosterone (especially when adjusted for SHBG as the free androgen index) is significantly higher in PCOS than in controls. Elevated androgens cause hirsutism and anovulation. Clinically, TT (and sometimes DHEA-S and androstenedione) is measured to confirm biochemical hyperandrogenism. High androgen levels also predict metabolic risk: e.g. each quartile rise in T multiplies metabolic-syndrome odds five-fold. These assays (preferably by sensitive LC-MS methods) are **widely used** in PCOS evaluation. **(Roudebush et al., 2008)**

Luteinizing Hormone (LH, LH:FSH ratio): PCOS is characterized by neuroendocrine dysregulation: increased GnRH pulse frequency elevates LH secretion. Consequently, LH (and the LH:FSH ratio) tends to be high in PCOS. High LH drives ovarian androgen production, reinforcing hyperandrogenism. Early studies often noted LH:FSH >2 as a PCOS indicator, and elevated LH remains a supportive finding. In practice, LH is measured (along with FSH and E2) to evaluate PCOS and rule out other causes (e.g. hypogonadism, pituitary issues). (However, current guidelines focus on androgen status and ovulatory function; LH is not required if hyperandrogenism is confirmed.) **(Roudebush et al., 2008)**

Infertility:

Male Infertility:

Follicle-Stimulating Hormone (FSH): A key marker of spermatogenic function. Elevated serum FSH indicates primary testicular (Sertoli cell) failure with impaired sperm production. In infertile men (especially with oligospermia/azoospermia), FSH is routinely measured. High FSH (often >10–15 mIU/mL) is specific for testicular failure, although mild FSH rises may be less sensitive. FSH testing is standard in the male infertility workup.

Luteinizing Hormone (LH): Evaluates Leydig cell (testosterone) function. In combination with testosterone, LH helps localize hypogonadism: high LH with low T signifies primary Leydig failure; low/normal LH with low T suggests central hypogonadism. LH is typically measured along with FSH and testosterone when endocrine causes of infertility are suspected.

Total Testosterone: Adequate testosterone is essential for spermatogenesis and libido. Low T impairs sperm production and sexual function. Serum TT is routinely obtained in infertile men to detect hypogonadism. (Endocrine disorders that lower T, such as pituitary tumors or hyperprolactinemia, must be excluded.)

Prolactin: Hyperprolactinemia can suppress GnRH, causing hypogonadism and infertility. Serum prolactin is checked if an infertile man has low libido, impotence, or abnormal semen counts without another explanation. Elevated prolactin is uncommon, but prolactin assay is **standard** when endocrine dysfunction is suspected.

Female Infertility:

Anti-Müllerian Hormone (AMH): Marker of ovarian reserve (follicle pool). Low AMH is a strong indicator of diminished ovarian reserve and reduced fertility; conversely, high AMH (beyond PCOS) can reflect polycystic ovaries. AMH is minimally variable across the cycle, so it is measured any time. In infertile women, AMH is widely used to gauge ovarian reserve and guide treatment (e.g. IVF stimulation). **(Ramasamy et al., 2025)**

FSH (Day-3) and Estradiol: Early follicular FSH is a classic ovarian reserve test. An elevated FSH on cycle day 3 (usually >10–15 mIU/mL) indicates diminished ovarian reserve. Simultaneous estradiol is measured to interpret FSH (e.g. high estradiol can suppress FSH). These measurements are performed early in the menstrual cycle; very high FSH is fairly specific for poor reserve. This test is **standard** in infertility workups. **(Scannell et al., 2025)**

Thyroid-Stimulating Hormone (TSH): Thyroid dysfunction can cause anovulation and infertility. TSH (often with free T4) is measured to rule out hypothyroidism or hyperthyroidism in all infertile women. Even subclinical hypothyroidism may impair the biological capacity or physical potential of an organism to produce offspring (fecundity). TSH is a **routine** screen in fertility evaluations. **(Natarajan et al., 2026)**

Prolactin: Hyperprolactinemia is a reversible cause of anovulation. Serum prolactin is tested in women with amenorrhea, oligomenorrhea or galactorrhea. Elevated prolactin (e.g. from a pituitary adenoma) suppresses GnRH and ovarian function. If elevated, it is treated medically. Prolactin measurement is standard in the endocrine workup of female infertility.**(Silvestris et al., 2019)**

Functional Nutrition and its Role:

Erectile Dysfunction

Functional nutrition for erectile dysfunction emphasizes metabolic and vascular support. Diets like the Mediterranean pattern, rich in vegetables, fruits, protein, olive oil, and fish, increase nitric oxide production (via arginine) and antioxidant defenses, improving lipid and glucose metabolism and reducing inflammation. Anti-inflammatory foods and micronutrient support (e.g. vitamins C/E, flavonoids, and omega-3 fats) help preserve endothelial function. Weight loss and enhanced insulin sensitivity further improve erectile physiology. In practice, antioxidant-rich

dietary interventions and supplements have been shown to significantly improve erectile function and related biomarkers in men with ED. **(Ferramosca & Zara, 2022)**

Polycystic Ovary Syndrome

In PCOS, functional nutrition targets insulin resistance and hormonal balance. Low glycemic-index whole-food diets (often Mediterranean-style) high in fiber, lean protein and omega-3 fats improve insulin sensitivity and lipid profiles, which in turn lower androgen levels and chronic inflammation. Ensuring adequate intake of key micronutrients (vitamin D, magnesium, zinc, inositol and B vitamins) is important, as many women with PCOS have deficiencies that worsen metabolic dysfunction. Anti-inflammatory phytonutrients (carotenoids, polyphenols, PUFAs from plants and fish) support ovulatory function and endothelial health. Together, these dietary strategies help normalize insulin, lipid and hormonal biomarkers in PCOS. **(Natarajan et al., 2026)**, **(Scannell et al., 2025)**

Female Infertility

Nutrition strongly influences female fertility via metabolic and reproductive pathways. In overweight women, adopting a Mediterranean-style diet and achieving healthy weight improves ovulation rates and IVF success. Critical micronutrients, especially folate, B-vitamins, vitamins C and E, and antioxidants from fruits and vegetables, support oocyte quality, embryo development and proper methylation. Limiting processed foods, refined sugars and saturated fats helps prevent insulin resistance and inflammation that can impair fertility. Overall, a nutrient-dense whole-food diet (with folic acid and antioxidant supplementation) tends to improve endocrine markers and enhance the chance of conception.**(Silvestris et al., 2019)**

Male Infertility

Nutritional interventions also benefit male fertility by improving sperm health and metabolic status. Diets low in processed foods and saturated fats, and rich in fruits, vegetables and healthy fats (particularly omega-3s), protect sperm from oxidative damage and support mitochondrial energy metabolism. Adequate micronutrients including zinc, selenium, L-arginine, L-carnitine, CoQ10 and vitamins C/E are linked to higher sperm count, motility and DNA integrity. Weight management and anti-inflammatory dietary patterns reduce metabolic stress on the reproductive system. Clinical studies show that antioxidant- and nutrient-rich diets or supplements can significantly enhance semen parameters and related fertility outcomes. **(Ferramosca & Zara, 2022)**

Conclusion

Erectile dysfunction, PCOS, and infertility are often treated as isolated reproductive conditions, yet the evidence consistently points toward a shared underlying driver: mitochondrial dysfunction. Impaired cellular energy production, oxidative stress, insulin resistance, and chronic inflammation disrupt endothelial signaling, steroid hormone synthesis, follicular maturation, and sperm function. In this light, reproductive disorders represent early manifestations of systemic metabolic imbalance rather than purely localized pathology.

The strong association between these conditions and type 2 diabetes, obesity, hypertension, dyslipidemia, and cardiovascular disease further reinforces this connection. High-energy tissues vascular endothelium, Leydig cells, granulosa cells, and oocytes are particularly vulnerable to mitochondrial impairment. Erectile dysfunction frequently precedes overt cardiovascular disease, and PCOS often predicts long-term metabolic syndrome, positioning reproductive dysfunction as a sentinel marker of bioenergetic decline.

Conventional therapies remain indispensable for symptom management and fertility support. However, most target downstream hormonal or vascular consequences without fully addressing upstream mitochondrial and metabolic instability. Functional nutrition offers a complementary, systems-based strategy aimed at restoring insulin sensitivity, reducing oxidative stress, improving inflammatory balance, and supporting micronutrient sufficiency. Dietary patterns such as the Mediterranean and low-glycemic approaches, along with targeted nutrient repletion and lifestyle modification, enhance mitochondrial efficiency and improve key reproductive biomarkers.

Reproductive health ultimately reflects cellular energy integrity. By integrating conventional medicine with mitochondrial-centered nutritional strategies, clinicians may not only improve fertility outcomes but also address the broader metabolic terrain that underlies chronic disease.

References:

Abu Shelbayeh, O., Arroum, T., Morris, S., & Busch, K. B. (2023). PGC-1α Is a Master Regulator of Mitochondrial Lifecycle and ROS Stress Response. *Antioxidants*, *12*(5), 1075. https://doi.org/10.3390/antiox12051075

Ahmadi Asouri, S., Asemi, R., Aghadavod, E., & Jamilian, M. (2024). The effect of coenzyme Q10 intake on metabolic profiles in women candidates for in-vitro fertilization: a randomised trial. *Annals of Medicine & Surgery*, *86*(6), 3378–3384. https://doi.org/10.1097/MS9.0000000000001732

Ahmed, W. S., Geethakumari, A. M., & Biswas, K. H. (2021). Phosphodiesterase 5 (PDE5): Structure-function regulation and therapeutic applications of inhibitors. *Biomedicine & Pharmacotherapy*, *134*, 111128. https://doi.org/10.1016/j.biopha.2020.111128

Albardan, L., Platat, C., & Kalupahana, N. S. (2024). Role of Omega-3 Fatty Acids in Improving Metabolic Dysfunctions in Polycystic Ovary Syndrome. *Nutrients*, *16*(17), 2961. https://doi.org/10.3390/nu16172961

Ardehjani, N. A., Agha-Hosseini, M., Nashtaei, M. S., Khodarahmian, M., Shabani, M., & Jabarpour, M. (2024). Resveratrol ameliorates mitochondrial biogenesis and reproductive outcomes in women with polycystic ovary syndrome undergoing assisted reproduction: a randomized, triple-blind, placebo-controlled clinical trial. *Journal of Ovarian Research*, *17*(1), 143. https://doi.org/10.1186/s13048-024-01470-9

Bao, Y., Miao, G., He, N., Bao, X., & Shi, Z. (2026). Melatonin as a Guardian of Mitochondria: Mechanisms and Therapeutic Potential in Neurodegenerative Diseases. *Biology*, *15*(2), 189. https://doi.org/10.3390/biology15020189

Bharali, M. D., Rajendran, R., Goswami, J., Singal, K., & Rajendran, V. (2022). Prevalence of Polycystic Ovarian Syndrome in India: A Systematic Review and Meta-Analysis. *Cureus*. https://doi.org/10.7759/cureus.32351

Bhatti, J. S., Bhatti, G. K., & Reddy, P. H. (2017). Mitochondrial dysfunction and oxidative stress in metabolic disorders — A step towards mitochondria based therapeutic strategies. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1863*(5), 1066–1077. https://doi.org/10.1016/j.bbadis.2016.11.010

Burnett, A. L. (2006). The Role of Nitric Oxide in Erectile Dysfunction: Implications for Medical Therapy. *The Journal of Clinical Hypertension*, *8*(s12), 53–62. https://doi.org/10.1111/j.1524-6175.2006.06026.x

Carson, S. A., & Kallen, A. N. (2021). Diagnosis and Management of Infertility. *JAMA*, *326*(1), 65. https://doi.org/10.1001/jama.2021.4788

Cyr, A. R., Huckaby, L. V., Shiva, S. S., & Zuckerbraun, B. S. (2020). Nitric Oxide and Endothelial Dysfunction. *Critical Care Clinics*, *36*(2), 307–321. https://doi.org/10.1016/j.ccc.2019.12.009

Di Meo, S., Reed, T. T., Venditti, P., & Victor, V. M. (2016). Role of ROS and RNS Sources in Physiological and Pathological Conditions. *Oxidative Medicine and Cellular Longevity*, *2016*(1). https://doi.org/10.1155/2016/1245049

Dube, R. (2016). Does endothelial dysfunction correlate with endocrinal abnormalities in patients with polycystic ovary syndrome? *Avicenna Journal of Medicine*, *06*(04), 91–102. https://doi.org/10.4103/2231-0770.191445

Eirin, A., Lerman, A., & Lerman, L. O. (2014). Mitochondrial injury and dysfunction in hypertension-induced cardiac damage. *European Heart Journal*, *35*(46), 3258–3266. https://doi.org/10.1093/eurheartj/ehu436

Engin, A. B. (2017). *What Is Lipotoxicity?* (pp. 197–220). https://doi.org/10.1007/978-3-319-48382-5_8

Ferramosca, A., & Zara, V. (2022). Diet and Male Fertility: The Impact of Nutrients and Antioxidants on Sperm Energetic Metabolism. *International Journal of Molecular Sciences*, *23*(5), 2542. https://doi.org/10.3390/ijms23052542

Foretz, M., Guigas, B., & Viollet, B. (2023). Metformin: update on mechanisms of action and repurposing potential. *Nature Reviews Endocrinology*, *19*(8), 460–476. https://doi.org/10.1038/s41574-023-00833-4

Forrester, S. J., Kikuchi, D. S., Hernandes, M. S., Xu, Q., & Griendling, K. K. (2018). Reactive Oxygen Species in Metabolic and Inflammatory Signaling. *Circulation Research*, *122*(6), 877–902. https://doi.org/10.1161/CIRCRESAHA.117.311401

Gómez del Val, A., Sánchez, A., Freire-Agulleiro, Ó., Martínez, M. P., Muñoz, M., Olmos, L., Medina, J. S., Comerma-Steffensen, S. G., Simonsen, U., Rivera, L., López, M., Contreras, C., & Prieto, D. (2025). Penile endothelial dysfunction, impaired redox metabolism and blunted mitochondrial bioenergetics in diet-induced obesity: Compensatory role of H2O2. *Free Radical Biology and Medicine*, *230*, 222–233. https://doi.org/10.1016/j.freeradbiomed.2025.02.004

Herman, T., Csehely, S., Orosz, M., Bhattoa, H. P., Deli, T., Torok, P., Lagana, A. S., Chiantera, V., & Jakab, A. (2023). Impact of Endocrine Disorders on IVF Outcomes: Results from a Large, Single-Centre, Prospective Study. *Reproductive Sciences*, *30*(6), 1878–1890. https://doi.org/10.1007/s43032-022-01137-0

Huffman, A. M., Rezq, S., Basnet, J., & Romero, D. G. (2023). Biomarkers in polycystic ovary syndrome. *Current Opinion in Physiology*, *36*, 100717. https://doi.org/10.1016/j.cophys.2023.100717

Janssen, J. J. E., Grefte, S., Keijer, J., & de Boer, V. C. J. (2019). Mito-Nuclear Communication by Mitochondrial Metabolites and Its Regulation by B-Vitamins. *Frontiers in Physiology*, *10*. https://doi.org/10.3389/fphys.2019.00078

Kim, M. E., & Lee, J. S. (2025). Advances in the Regulation of Inflammatory Mediators in Nitric Oxide Synthase: Implications for Disease Modulation and Therapeutic Approaches. *International Journal of Molecular Sciences*, *26*(3), 1204. https://doi.org/10.3390/ijms26031204

Kirichenko, T. V., Markina, Y. V., Bogatyreva, A. I., Tolstik, T. V., Varaeva, Y. R., & Starodubova, A. V. (2022). The Role of Adipokines in Inflammatory Mechanisms of Obesity. *International Journal of Molecular Sciences*, *23*(23), 14982. https://doi.org/10.3390/ijms232314982

Lipke, K., Kubis-Kubiak, A., & Piwowar, A. (2022). Molecular Mechanism of Lipotoxicity as an Interesting Aspect in the Development of Pathological States—Current View of Knowledge. *Cells*, *11*(5), 844. https://doi.org/10.3390/cells11050844

Liu, C., Gao, Y., Ji, J., Sun, C., & Chen, M. (2023). Association between inflammatory indexes and erectile dysfunction in U.S. adults: National Health and Nutrition Examination Survey 2001-2004. *Sexual Medicine*, *11*(4). https://doi.org/10.1093/sexmed/qfad045

Liu, H., Jin, L., Wang, X., Shi, J., He, Y., Sun, N., & Yang, F. (2025). Reactive oxygen species in polycystic ovary syndrome: Mechanistic insights into pathogenesis and therapeutic opportunities. *Redox Biology*, *85*, 103776. https://doi.org/10.1016/j.redox.2025.103776

Lucas, A., Herrmann, S., & Lucas, M. (2022). The role of endocrine-disrupting phthalates and bisphenols in cardiometabolic disease: the evidence is mounting. *Current Opinion in Endocrinology, Diabetes & Obesity*, *29*(2), 87–94. https://doi.org/10.1097/MED.0000000000000712

Napolitano, G., Fasciolo, G., & Venditti, P. (2021). Mitochondrial Management of Reactive Oxygen Species. *Antioxidants*, *10*(11), 1824. https://doi.org/10.3390/antiox10111824

Natarajan, M., E., S. H., & Nataraj, R. (2026). Micronutrients in polycystic ovary syndrome: molecular pathways, deficiencies, and therapeutic potential. *Frontiers in Endocrinology*, *17*. https://doi.org/10.3389/fendo.2026.1766838

Odetayo, A. F., & Olayaki, L. A. (2023). Omega 3 fatty acid improves sexual and erectile function in BPF-treated rats by upregulating NO/cGMP signaling and steroidogenic enzymes activities. *Scientific Reports*, *13*(1), 18060. https://doi.org/10.1038/s41598-023-45344-4

Okobi, O. E. (2021). A Systemic Review on the Association Between Infertility and Sexual Dysfunction Among Women Utilizing Female Sexual Function Index as a Measuring Tool. *Cureus*. https://doi.org/10.7759/cureus.16006

Oteri, V., Galeano, F., Panebianco, S., Piticchio, T., Le Moli, R., & Frittitta, L. (2024). Influence of Mediterranean Diet on Sexual Function in People with Metabolic Syndrome: A Narrative Review. *Nutrients*, *16*(19), 3397. https://doi.org/10.3390/nu16193397

Paneni, F. (2015). Role of oxidative stress in endothelial insulin resistance. *World Journal of Diabetes*, *6*(2), 326. https://doi.org/10.4239/wjd.v6.i2.326

Pastuszak, A. W. (2014). Current Diagnosis and Management of Erectile Dysfunction. *Current Sexual Health Reports*, *6*(3), 164–176. https://doi.org/10.1007/s11930-014-0023-9

Porav-Hodade, D., Gherasim, R. D., Kosovski, I. B., Voidazan, T. S., Crisan, N., Bogdan, P., Galis, R., Feciche, B. O., Ilona, M. O. K., & Todea-Moga, C. (2025). Hormones, Age, and Erectile Dysfunction: Should Routine Testing Be Part of the Initial Evaluation? *Diagnostics*, *15*(3), 294. https://doi.org/10.3390/diagnostics15030294

Ramasamy, R., Bhattacharyya, S., Kohn, T. P., & Miller, L. E. (2025). Antioxidant Supplementation for Erectile Dysfunction: Systematic Review and Meta-Analysis of Double-Blind, Randomized, Placebo-Controlled Trials. *The World Journal of Men's Health*, *43*(1), 81. https://doi.org/10.5534/wjmh.230280

Reddam, A., McLarnan, S., & Kupsco, A. (2022). Environmental Chemical Exposures and Mitochondrial Dysfunction: a Review of Recent Literature. *Current Environmental Health Reports*, *9*(4), 631–649. https://doi.org/10.1007/s40572-022-00371-7

Rizk, P. J., Kohn, T. P., Pastuszak, A. W., & Khera, M. (2017). Testosterone therapy improves erectile function and libido in hypogonadal men. *Current Opinion in Urology*, *27*(6), 511–515. https://doi.org/10.1097/MOU.0000000000000442

Rojas, J., Chávez, M., Olivar, L., Rojas, M., Morillo, J., Mejías, J., Calvo, M., & Bermúdez, V. (2014). Polycystic Ovary Syndrome, Insulin Resistance, and Obesity: Navigating the Pathophysiologic Labyrinth. *International Journal of Reproductive Medicine*, *2014*, 1–17. https://doi.org/10.1155/2014/719050

Roudebush, W. E., Kivens, W. J., & Mattke, J. M. (2008). Biomarkers of Ovarian Reserve. *Biomarker Insights*, *3*, BMI.S537. https://doi.org/10.4137/BMI.S537

Rył, A., Ciosek, Ż., Szylińska, A., Jurewicz, A., Bohatyrewicz, A., & Rotter, I. (2024a). Concentrations of Bioelements (Zn, Cu, Fe, Cr, Mg, Mn) in Serum and Bone Tissue of Aging Men Undergoing Hip Arthroplasty: Implications for Erectile Dysfunction. *Biomolecules*, *14*(5), 565. https://doi.org/10.3390/biom14050565

Rył, A., Ciosek, Ż., Szylińska, A., Jurewicz, A., Bohatyrewicz, A., & Rotter, I. (2024b). Concentrations of Bioelements (Zn, Cu, Fe, Cr, Mg, Mn) in Serum and Bone Tissue of Aging Men Undergoing Hip Arthroplasty: Implications for Erectile Dysfunction. *Biomolecules*, *14*(5), 565. https://doi.org/10.3390/biom14050565

Scannell, N., Villani, A., Moran, L., & Mantzioris, E. (2025). The potential role of the Mediterranean diet for the treatment and management of polycystic ovary syndrome: a review of the pathophysiological mechanisms and clinical evidence. *Proceedings of the Nutrition Society*, *84*(2), 176–187. https://doi.org/10.1017/S0029665124007584

Sergi, D., Naumovski, N., Heilbronn, L. K., Abeywardena, M., O'Callaghan, N., Lionetti, L., & Luscombe-Marsh, N. (2019). Mitochondrial (Dys)function and Insulin Resistance: From Pathophysiological Molecular Mechanisms to the Impact of Diet. *Frontiers in Physiology*, *10*. https://doi.org/10.3389/fphys.2019.00532

Shaughnessy, D. T., McAllister, K., Worth, L., Haugen, A. C., & Tyson, F. L. (2014). Mitochondria, Energetics, Epigenetics, and Cellular Responses to Stress. *Environmental Health Perspectives*, *122*(12), 1271–1278. https://doi.org/10.1289/ehp.1408418

Siemers, K. M., Klein, A. K., & Baack, M. L. (2023). Mitochondrial Dysfunction in PCOS: Insights into Reproductive Organ Pathophysiology. *International Journal of Molecular Sciences*, *24*(17), 13123. https://doi.org/10.3390/ijms241713123

Silvestris, E., Lovero, D., & Palmirotta, R. (2019). Nutrition and Female Fertility: An Interdependent Correlation. *Frontiers in Endocrinology*, *10*. https://doi.org/10.3389/fendo.2019.00346

Singh, S., Pal, N., Shubham, S., Sarma, D. K., Verma, V., Marotta, F., & Kumar, M. (2023). Polycystic Ovary Syndrome: Etiology, Current Management, and Future Therapeutics. *Journal of Clinical Medicine*, *12*(4), 1454. https://doi.org/10.3390/jcm12041454

Stamerra, C. A., Di Giosia, P., Giorgini, P., Ferri, C., Sukhorukov, V. N., & Sahebkar, A. (2022). [Retracted] Mitochondrial Dysfunction and Cardiovascular Disease: Pathophysiology and Emerging Therapies. *Oxidative Medicine and Cellular Longevity*, *2022*(1). https://doi.org/10.1155/2022/9530007

Tang, N., Hong, F., Hao, W., Yu, T.-T., Wang, G.-G., & Li, W. (2022). Riboflavin ameliorates mitochondrial dysfunction via the AMPK/PGC1α/HO-1 signaling pathway and attenuates carbon tetrachloride-induced liver fibrosis in rats. *Experimental and Therapeutic Medicine*, *24*(4), 608. https://doi.org/10.3892/etm.2022.11545

Tharayil, S. P., & Shukla, P. (2025). Connecting the Dots: Mitochondrial Dysfunction, PCOS, and Insulin Resistance—Insights and Therapeutic Advances. *International Journal of Molecular Sciences*, *26*(13), 6233. https://doi.org/10.3390/ijms26136233

Velissariou, M., Athanasiadou, C. R., Diamanti, A., Lykeridou, A., & Sarantaki, A. (2025). The impact of intermittent fasting on fertility: A focus on polycystic ovary syndrome and reproductive outcomes in Women-A systematic review. *Metabolism Open*, *25*, 100341. https://doi.org/10.1016/j.metop.2024.100341

Verma, A. K. (2016). Anti-Mullerian Hormone: A Marker of Ovarian Reserve and its Association with Polycystic Ovarian Syndrome. *JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH*. https://doi.org/10.7860/JCDR/2016/20370.8988

Vlaicu, A. G., Mirvald, C., Najjar, S., Garaz, R., Tsaur, I., Sinescu, I., & Surcel, C. (2026). Intracavernous Injection Therapy as Second-Line Treatment for ED After Radical Prostatectomy: A Literature Review. *Medicina*, *62*(1), 111. https://doi.org/10.3390/medicina62010111

Wu, J., Fan, L., Yang, X., Zhang, S., & Zheng, W. (2025). Association of erectile dysfunction and daily food thiamin intake among men in the USA. *BMJ Nutrition, Prevention & Health*, *8*(2), 632–638. https://doi.org/10.1136/bmjnph-2024-000911

Yafi, F. A., Jenkins, L., Albersen, M., Corona, G., Isidori, A. M., Goldfarb, S., Maggi, M., Nelson, C. J., Parish, S., Salonia, A., Tan, R., Mulhall, J. P., & Hellstrom, W. J. G. (2016). Erectile dysfunction. *Nature Reviews Disease Primers*, *2*(1), 16003. https://doi.org/10.1038/nrdp.2016.3

Yan, X., Ma, D., Li, R., Xu, J., Zou, Y., & He, M. (2025). The role of mitochondrial dysfunction in ovarian granulosa cells in polycystic ovary syndrome. *Endocrine Connections*, *14*(7). https://doi.org/10.1530/EC-25-0186

Zhang, A., Wang, J., Zhao, Y., He, Y., & Sun, N. (2024a). Intermittent fasting, fatty acid metabolism reprogramming, and neuroimmuno microenvironment: mechanisms and application prospects. *Frontiers in Nutrition*, *11*. https://doi.org/10.3389/fnut.2024.1485632

Zhang, A., Wang, J., Zhao, Y., He, Y., & Sun, N. (2024b). Intermittent fasting, fatty acid metabolism reprogramming, and neuroimmuno microenvironment: mechanisms and application prospects. *Frontiers in Nutrition*, *11*. https://doi.org/10.3389/fnut.2024.1485632

Zhang, X., Zhang, L., & Xiang, W. (2025). The impact of mitochondrial dysfunction on ovarian aging. *Journal of Translational Medicine*, *23*(1), 211. https://doi.org/10.1186/s12967-025-06223-w

Zhao, J., Dong, L., Lin, Z., Sui, X., Wang, Y., & Li, L. (2023). Effects of selenium supplementation on Polycystic Ovarian Syndrome: a systematic review and meta-analysis on randomized clinical trials. *BMC Endocrine Disorders*, *23*(1), 33. https://doi.org/10.1186/s12902-023-01286-6

Zhu, H., Chen, S., Ye, Q., Lin, W., Li, T., Xu, Z., & Huang, Z. (2024). Association between composite dietary antioxidant index and erectile dysfunction among American adults: a cross-sectional study. *Scientific Reports*, *14*(1), 21230. https://doi.org/10.1038/s41598-024-72157-w