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Astaxanthin Supplementation in Polycystic Ovary Syndrome: Effects on Oxidative Stress, Inflammation, Metabolic Dysfunction, and Assisted Reproductive Outcomes

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Abstract
Background. Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine-metabolic disorder characterized by hyperandrogenism, ovulatory dysfunction, polycystic ovarian morphology, insulin resistance, and chronic low-grade inflammation. Increasing evidence suggests that oxidative stress, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and dysregulated apoptosis contribute substantially to both the reproductive and metabolic manifestations of PCOS. Astaxanthin, a xanthophyll carotenoid with potent antioxidant and anti-inflammatory properties, has recently emerged as a candidate adjunctive therapy in this setting.
Aim. This review synthesizes current evidence regarding astaxanthin supplementation in PCOS, with emphasis on mechanistic plausibility, metabolic endpoints, inflammatory and oxidative stress biomarkers, and assisted reproductive technology (ART) outcomes. Recent randomized clinical trials suggest that astaxanthin may improve selected biochemical and molecular parameters, including total antioxidant capacity, lipid peroxidation markers, inflammatory cytokines, and expression of genes implicated in ER stress and apoptosis. In infertile women with PCOS undergoing ART, astaxanthin has been associated with improvements in intermediate reproductive outcomes such as oocyte maturity, embryo quality, and the number of frozen or high-quality embryos. However, benefits for hard clinical endpoints, especially chemical pregnancy, clinical pregnancy, and live birth, remain inconsistent.

Material and methods. A systematic search was conducted across PubMed and Scopus. The analysis included randomized trials, systematic reviews and clinical guidelines.

Conclusions. Existing data support a biologically plausible and clinically promising, but not yet definitive, role for astaxanthin as an adjunctive nutraceutical in PCOS. Larger multicenter randomized trials with standardized outcomes, rigorous phenotyping, and longer follow-up are needed before astaxanthin can be recommended as part of guideline-directed PCOS management.

Key words: astaxanthin; polycystic ovary syndrome; oxidative stress; inflammation; insulin resistance; assisted reproductive technology

1. Introduction

Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders in women of reproductive age and remains a major cause of anovulatory infertility. It is increasingly recognized as a lifelong multisystem condition involving reproductive, metabolic, dermatologic, and psychological domains. The syndrome is typically defined by combinations of oligo-anovulation, hyperandrogenism, and polycystic ovarian morphology, although considerable interindividual variability exists in clinical presentation and severity [1,2].

Beyond reproductive dysfunction, PCOS is strongly associated with insulin resistance, compensatory hyperinsulinemia, dyslipidemia, obesity, impaired glucose tolerance, type 2 diabetes mellitus, and increased long-term cardiometabolic risk [1-3]. Mechanistically, PCOS is not a purely ovarian disorder. Rather, it involves altered gonadotropin secretion, adipose-tissue dysfunction, oxidative stress, low-grade inflammation, mitochondrial abnormalities, and intraovarian disturbances affecting folliculogenesis, granulosa-cell function, oocyte competence, and embryo quality [1-4].

Oxidative stress is increasingly viewed as a pathophysiological bridge between metabolic dysfunction and reproductive impairment in PCOS. Excess reactive oxygen species may promote lipid peroxidation, mitochondrial injury, inflammatory signaling, endoplasmic reticulum stress, and apoptosis. These processes may impair ovarian microenvironment homeostasis and contribute to abnormal steroidogenesis, follicular arrest, and reduced developmental competence of oocytes and embryos [3,4].

Astaxanthin is a naturally occurring keto-carotenoid found in microalgae, yeast, salmonids, shrimp, trout, and krill. Its molecular structure allows it to interact with lipid membranes and exert antioxidant and membrane-stabilizing effects. Experimental and clinical literature suggests that astaxanthin may modulate Nrf2/ARE, NF-kB, PI3K/AKT, MAPK, inflammatory, oxidative-stress, and apoptosis-related pathways [5,6]. These properties make astaxanthin a biologically plausible adjunctive intervention in PCOS, particularly in phenotypes characterized by oxidative-inflammatory burden and suboptimal ART outcomes.

The purpose of this review is to critically examine the mechanistic rationale and current clinical evidence for astaxanthin supplementation in PCOS, with special attention to metabolic disturbances, ovarian biology, ART outcomes, and the translational gap between surrogate biomarker improvement and clinically meaningful endpoints.

2. Research materials and methods

This article was designed as a structured narrative review evaluating the potential role of astaxanthin supplementation in PCOS. The review focuses on oxidative stress, inflammation, metabolic dysfunction, granulosa-cell biology, endoplasmic reticulum stress, apoptosis, oocyte competence, embryo quality, and ART-related outcomes.

A targeted literature search was conducted in PubMed and Scopus. The search focused primarily on publications from the last 15 years, while older sources were considered when they provided relevant mechanistic or clinical context. Search terms included combinations of: “astaxanthin,” “polycystic ovary syndrome,” “PCOS,” “oxidative stress,” “inflammation,” “insulin resistance,” “granulosa cells,” “endoplasmic reticulum stress,” “apoptosis,” “oocyte maturation,” “embryo quality,” “assisted reproductive technology,” “IVF,” and “ICSI.” Additional relevant publications were identified from the reference lists of included studies and recent reviews.

Eligible publications included randomized clinical trials, controlled clinical studies, observational studies, mechanistic human studies, animal experiments, systematic reviews, meta-analyses, and major guideline documents relevant to PCOS pathophysiology or management. Priority was given to studies directly assessing astaxanthin supplementation in women with PCOS, particularly those reporting biochemical, molecular, metabolic, or reproductive outcomes. Studies were also considered when they provided mechanistic context for astaxanthin activity, including antioxidant, anti-inflammatory, anti-apoptotic, mitochondrial, or endoplasmic-reticulum stress-related effects.

The main outcomes extracted and narratively synthesized included oxidative-stress markers, antioxidant capacity, inflammatory cytokines, insulin-resistance indices, lipid-profile parameters, granulosa-cell gene and protein expression, apoptosis-related mediators, oocyte maturity, embryo quality, number of transferable or frozen embryos, fertilization outcomes, chemical pregnancy, clinical pregnancy, and live birth when available. Because of heterogeneity in study design, intervention dose, treatment duration, population characteristics, measured biomarkers, and reproductive endpoints, no quantitative meta-analysis was performed. This review relies on statistical results reported in the original studies and meta-analyses; no independent statistical re-analysis was performed.

AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

3. Research results

3.1. Pathophysiological basis for astaxanthin use in PCOS

Oxidative stress refers to an imbalance between oxidant generation and antioxidant defense, resulting in redox dysregulation, cellular injury, and altered intracellular signaling. In PCOS, oxidative stress may arise from obesity, hyperglycemia, insulin resistance, lipotoxicity, mitochondrial dysfunction, chronic inflammation, and

androgen excess [1,3]. Elevated oxidative-stress biomarkers, including malondialdehyde, and impaired antioxidant defenses have been documented in subsets of women with PCOS.

PCOS is also commonly characterized by chronic low-grade inflammation. Increased circulating concentrations of interleukin-6, tumor necrosis factor-alpha, C-reactive protein, interleukin-1 beta, interleukin-8, and related inflammatory mediators have been described, particularly in metabolically affected phenotypes [1,3]. Although adiposity may amplify inflammatory activation, inflammation is not limited to obese phenotypes and may interact with ovarian and systemic metabolic disturbances.

Mitochondria are central to oocyte maturation, spindle integrity, ATP generation, and apoptotic regulation. Mitochondrial dysfunction has been implicated in PCOS pathogenesis, including altered mitochondrial biogenesis, abnormal mitochondrial DNA profiles, and increased reactive oxygen species production [3]. Because oocytes are highly energy-dependent, even modest redox imbalance may adversely influence oocyte competence and embryo development.

Endoplasmic reticulum stress develops when protein-folding demand exceeds endoplasmic reticulum capacity, triggering the unfolded protein response. In PCOS, endoplasmic reticulum stress has been linked to granulosa-cell dysfunction, inflammation, apoptosis, and impaired folliculogenesis. Markers such as GRP78, CHOP, XBP1, ATF4, and related proteins have been evaluated in this context [4,8].

Dysregulated apoptosis is another mechanism relevant to PCOS-associated follicular dysfunction. Altered expression of pro-apoptotic mediators such as BAX, DR5, and caspases, together with anti-apoptotic mediators such as BCL2, may contribute to abnormal follicular development and reduced oocyte competence [9].

Insulin resistance remains one of the most clinically relevant features of PCOS. Hyperinsulinemia augments ovarian androgen production, suppresses sex hormone-binding globulin, and worsens metabolic stress. It may also be associated with poorer ART outcomes, abnormal endometrial receptivity, and reduced reproductive efficiency [1,2,11].

Astaxanthin is a lipid-soluble xanthophyll carotenoid chemically designated as 3,3'-dihydroxy-beta,beta'-carotene-4,4'-dione. Its architecture includes polar ionone rings at both ends and a long conjugated polyene chain, allowing interaction across phospholipid bilayers and efficient quenching of singlet oxygen and other reactive oxygen species [5,6].

Natural astaxanthin is derived predominantly from Haematococcus pluvialis, although it is also found in other microorganisms and marine organisms. Compared with several other carotenoids, astaxanthin demonstrates strong free-radical scavenging and membrane-stabilizing properties [5].

Preclinical work suggests that astaxanthin may reduce lipid peroxidation, enhance endogenous antioxidant enzyme activity, activate Nrf2/ARE signaling, inhibit NF-kB-mediated inflammation, modulate PI3K/AKT and MAPK pathways, attenuate endoplasmic reticulum stress, reduce apoptosis, and improve mitochondrial function [5,6]. This profile is relevant to PCOS because oxidative stress, inflammatory signaling, endoplasmic reticulum stress, and granulosa-cell injury converge to influence follicular development and metabolic dysfunction.

3.2. Preclinical and mechanistic evidence relevant to PCOS

Preclinical models support the biological plausibility of astaxanthin use in PCOS. In experimental PCOS models, astaxanthin has been associated with reduced ovarian oxidative stress, lower inflammatory marker expression, and improved histopathological features.

Experimental work in granulosa cells and animal PCOS models also suggests that astaxanthin may reduce reactive oxygen species burden, decrease apoptosis, and improve ovarian morphology [7]. These observations are consistent with human mechanistic studies in which astaxanthin modulated endoplasmic reticulum stress and apoptosis-related gene expression in granulosa cells and peripheral blood mononuclear cells [4,8,9].3.5 Immunosuppressive treatment

3.3. Clinical evidence in women with PCOS

One randomized controlled trial in infertile women with PCOS undergoing ART found that 8 mg/day astaxanthin for 40 days increased serum catalase and total antioxidant capacity and upregulated Nrf2, HO-1, and NQO1 expression in granulosa cells. The same study reported improvements in MII oocyte rate and high-quality embryo rate, although chemical and clinical pregnancy rates did not differ significantly between groups [10].

A triple-blind randomized clinical trial reported that 12 mg/day astaxanthin for 8 weeks reduced fasting blood sugar, HOMA-IR, malondialdehyde, LDL cholesterol, and total cholesterol/HDL cholesterol ratio, while increasing total antioxidant capacity and HDL cholesterol in infertile women with PCOS. Although some findings were attenuated after adjustment, the overall pattern was compatible with reduced oxidative burden and improved metabolic status [11].

Another randomized clinical trial demonstrated that astaxanthin treatment reduced expression of endoplasmic reticulum stress-related genes, including GRP78, CHOP, and XBP1, in granulosa cells from women with PCOS, with corresponding reductions in GRP78 and CHOP protein levels. These molecular findings support the concept that astaxanthin may modulate the unfolded protein response and reduce stress burden in the ovarian microenvironment [4].

A subsequent randomized study evaluating peripheral blood mononuclear cells showed that 12 mg/day astaxanthin for 8 weeks reduced expression of CHOP, XBP1, ATF4, and DR5, with borderline or non-significant reductions in selected additional markers. In parallel, inflammatory mediators including tumor necrosis factor-alpha, interleukin-18, and interleukin-6 were significantly reduced, whereas C-reactive protein was not clearly changed [8].

In a randomized clinical trial focused on apoptotic signaling, astaxanthin supplementation was associated with reduced DR5 and BAX expression and increased BCL2 expression in granulosa cells, together with favorable shifts in follicular-fluid and serum apoptosis-related factors. Although not all endpoints reached statistical significance, the overall direction suggested a shift toward an anti-apoptotic profile [9].

The most clinically relevant question is whether these molecular and biochemical changes translate into improved fertility outcomes. Across available PCOS studies, astaxanthin has been associated with higher MII oocyte rates, improved oocyte maturity, increased high-quality embryo rates, and increased numbers of transferable or frozen embryos [4,10,12]. However, evidence for improved chemical pregnancy, clinical pregnancy, and live birth remains inconsistent and underpowered.

A randomized clinical trial in PCOS patients undergoing ART reported that astaxanthin decreased pro-inflammatory cytokines and improved selected reproductive outcomes, including numbers of retrieved oocytes, MII oocytes, and frozen embryos, but did not demonstrate a clear pregnancy benefit [12]. A retrospective study in women with PCOS undergoing IVF/ICSI reported improvements in insulin resistance, hormone levels,

embryo quality, and pregnancy-related outcomes after 3 months of compound nutrient supplementation containing astaxanthin. However, causal inference is limited by the non-randomized design and the use of a compound formulation rather than isolated astaxanthin.

3.5. Evidence from systematic reviews and broader reproductive literature

A systematic review and meta-analysis focused on female fertility and reproductive outcomes concluded that astaxanthin supplementation may improve oocyte maturation rate and follicular-fluid total antioxidant capacity, while not clearly improving most pregnancy outcomes [17]. This supports the interpretation that astaxanthin has measurable effects on reproductive biology, but that robust evidence for improved live birth or sustained clinical pregnancy has not yet been established.

Evidence from broader metabolic literature, including studies in diabetes and prediabetes, suggests that astaxanthin may improve selected oxidative-stress and metabolic parameters in some populations [13-15]. However, extrapolation to PCOS should be cautious because PCOS involves distinct reproductive, endocrine, and ovarian microenvironmental mechanisms.

Table 1. Key studies of astaxanthin supplementation or astaxanthin-related interventions relevant to PCOS

Study	Design / population	Dose and duration	Main findings	Main limitation
Gharaei et al. [10]	Randomized controlled trial; infertile women with PCOS undergoing ART	8 mg/day for 40 days	Increased serum catalase and total antioxidant capacity; upregulated granulosa-cell antioxidant gene expression; improved MII oocyte and high-quality embryo rates	No clear improvement in chemical or clinical pregnancy
Jabarpour et al. [11]	Triple-blind randomized clinical trial; infertile women with PCOS	12 mg/day for 8 weeks	Reduced fasting blood sugar, HOMA-IR, malondialdehyde, LDL cholesterol, and TC/HDL-C; increased total antioxidant capacity and HDL cholesterol	Some effects attenuated after adjustment; short follow-up
Jabarpour et al. [4]	Randomized clinical trial; women with PCOS	12 mg/day for 60 days	Reduced GRP78, CHOP, and XBP1 expression in granulosa cells; improved selected ovarian microenvironment markers	Molecular endpoints predominate; limited power for pregnancy outcomes

Study	Design / population	Dose and duration	Main findings	Main limitation
Jabarpour et al. [8]	Randomized clinical trial; women with PCOS	12 mg/day for 8 weeks	Reduced TNF-alpha, IL-18, IL-6, and selected ER stress-apoptosis gene-expression markers in PBMCs	Systemic PBMC markers may not fully reflect ovarian tissue effects
Jabarpour et al. [9]	Randomized clinical trial; women with PCOS	12 mg/day for 8 weeks	Reduced pro-apoptotic signaling and increased BCL2 expression in granulosa cells	Exploratory molecular endpoints; modest sample size
Fereidouni et al. [12]	Randomized clinical trial; infertile PCOS patients undergoing ART	6 mg/day for 8 weeks	Reduced pro-inflammatory cytokines and improved selected ART laboratory outcomes	No definitive clinical pregnancy or live-birth benefit
Fu et al. [16]	Retrospective study; PCOS patients undergoing IVF/ICSI	Compound nutrient for 3 months	Reported improvements in insulin resistance, hormones, embryo quality, and pregnancy-related outcomes	Non-randomized design and compound formulation limit causal interpretation

4. Discussion

The central interpretive issue in the astaxanthin-PCOS literature is the distinction between biological activity and clinically transformative efficacy. Available randomized trials suggest that astaxanthin is biologically active in women with PCOS, especially with respect to oxidative-stress biomarkers, inflammatory mediators, endoplasmic reticulum stress, apoptosis-related gene expression, and selected ART laboratory outcomes [4,8-12]. These signals are mechanistically coherent because oxidative stress, inflammatory activation, and granulosa-cell dysfunction are interwoven components of PCOS pathophysiology.

However, clinical efficacy cannot be inferred solely from biomarker normalization. The most important translational question is whether these molecular changes are large enough, durable enough, and tissue-relevant enough to alter patient-important outcomes, including ovulation, sustained metabolic improvement, cumulative pregnancy rate, miscarriage risk, and live birth. At present, this remains uncertain. The literature most consistently supports improvement in intermediate ART outcomes, especially oocyte maturity and embryo-quality metrics, whereas evidence for downstream pregnancy endpoints remains inconsistent [10,12,17].

This discrepancy may have several explanations. First, most available studies are underpowered for reproductive endpoints. Second, implantation and ongoing pregnancy depend on numerous factors beyond oocyte competence, including sperm quality, embryo aneuploidy, endometrial receptivity, luteal support, and stimulation-protocol heterogeneity. Third, intervention periods of 40 days to 12 weeks may be too short to remodel the broader endocrine-metabolic environment of PCOS. Therefore, the absence of consistent pregnancy benefit should be interpreted as evidence that current trials are not decisive, rather than as definitive proof of inefficacy.

Phenotypic heterogeneity also matters. PCOS is not a single biological entity. Lean hyperandrogenic phenotypes, obese insulin-resistant phenotypes, infertility-dominant ART populations, and metabolically severe phenotypes may not respond equally to antioxidant therapy. It is plausible that astaxanthin will eventually find a role in responder-enriched subgroups, such as women with insulin resistance, elevated oxidative-inflammatory burden, adverse follicular-fluid profiles, or repeated poor ART laboratory outcomes. This hypothesis requires formal testing in stratified trials.

Astaxanthin should also be situated within current PCOS management rather than viewed in isolation. Contemporary evidence-based management prioritizes lifestyle intervention, weight reduction where appropriate, cycle regulation, treatment of hyperandrogenic symptoms, and fertility-directed strategies such as letrozole or ART. Metformin remains relevant for metabolic features and selected reproductive contexts [2]. Against this background, astaxanthin should currently be conceptualized, if used at all, as an investigational adjunct rather than an alternative to established therapy.

5. Future research directions

Future studies should move beyond proof-of-concept biomarker trials toward multicenter, randomized, placebo-controlled, adequately powered, and phenotype-stratified designs. At minimum, trials should standardize diagnostic criteria, supplement formulation, dose, duration of therapy, co-interventions, and outcome hierarchy. Studies should explicitly define whether the primary aim is metabolic improvement, ovulation restoration, or ART outcome enhancement, because each aim requires different populations and sample-size assumptions.

For ART-focused trials, preferred primary endpoints should move beyond isolated embryo-quality metrics toward cumulative live birth, ongoing pregnancy, or at least clinical pregnancy per initiated cycle. Secondary endpoints may include oocyte maturity, embryo morphology, follicular-fluid cytokines, oxidative-stress biomarkers, and granulosa-cell transcriptomic measures. For non-ART PCOS populations, priority outcomes should include ovulation frequency, menstrual cyclicity, androgen-related symptoms, insulin resistance, cardiometabolic markers, and quality of life.

Mechanistic studies should further examine mitochondrial bioenergetics, endometrial receptivity, embryo developmental competence, systemic versus ovarian compartment effects, and interactions with metformin, inositols, lifestyle intervention, and ovarian stimulation protocols. Translational research should also address pharmacokinetics, formulation science, tissue bioavailability, and the relationship between biochemical response and clinically meaningful benefit.

6. Conclusions

Astaxanthin is a promising nutraceutical candidate in PCOS because its antioxidant, anti-inflammatory, anti-apoptotic, and endoplasmic-reticulum-stress-modulating properties align with several important pathogenic mechanisms of the syndrome. Clinical trials to date suggest that astaxanthin may improve oxidative-stress indices, inflammatory markers, insulin resistance, and selected intermediate ART outcomes, including oocyte maturity and embryo quality. Nevertheless, current evidence does not establish a consistent benefit for definitive reproductive endpoints such as clinical pregnancy or live birth.

Accordingly, astaxanthin should currently be regarded as an investigational adjunct rather than a standard component of PCOS management. Its future clinical role will depend on whether larger, independent,

methodologically rigorous studies can confirm meaningful reproductive and metabolic benefits beyond surrogate biomarker improvement.

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