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Policy Brief

Antioxidant therapy for endometriosis pain: A policy brief on evidence, gaps, and future directions

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Abstract

Antioxidant therapies, accessible and cost-effective, present a viable strategy for enhancing health equity in endometriosis management while potentially decreasing dependence on expensive treatments. By addressing oxidative stress, a central factor in disease advancement compounds like vitamins C, E, and D, N-acetylcysteine, curcumin, resveratrol, and melatonin offer non-hormonal avenues for symptom relief. Evidence indicates pain reduction, notably with melatonin, yet studies are small, varied, and inconclusive regarding lesion reduction. Policy recommendations emphasize funding robust multicenter trials, cautiously integrating antioxidants into clinical guidelines, educating clinicians, and empowering patients through awareness campaigns. Their low cost and safety profile make antioxidants a compelling adjunct, aligning with patient needs and promoting access in resource-limited settings. Targeted investment in biomarker research could further refine personalized treatment, improving outcomes for millions living with this chronic condition.

Keywords: Endometriosis, Chronic pelvic pain, Antioxidants, Oxidative stress, Policy, Dietary supplements, non-hormonal therapy.

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Executive summary: Endometriosis represents a significant global health challenge, affecting approximately 10% of reproductive-aged women worldwide (1), with an estimated 190 million individuals suffering from its debilitating symptoms (2). Diagnostic delays averaging 7–12 years and limited efficacy of current treatments NSAIDs, hormonal therapies, and surgery, underscore a critical health challenge (3). Mounting evidence implicates oxidative stress as a key mechanism, opening the door to adjuvant antioxidant-based therapies (4, 5). Several antioxidant agents including vitamins C and E (6, 7), N-acetylcysteine (NAC) (8), resveratrol (9), and melatonin (10-12) have shown promise in reducing inflammation, pain, or lesion size in preclinical or early clinical studies (13). Among these, melatonin stands out for its dual antioxidant and analgesic properties and has demonstrated symptom relief in human trials (11). This policy brief summarizes current scientific findings and calls for policy action to support research, integration into clinical guidelines, and development of personalized adjuvant treatment approaches.

The problem: chronic pelvic pain and gaps in current therapy: Endometriosis-related chronic pelvic pain and dysmenorrhea often persist despite standard treatments (14). According to the American College of Obstetricians and Gynecologists (ACOG), first-line management typically involves NSAIDs and combined oral contraceptives (COCs) or progestins, which act through anti-inflammatory and hormonal suppression mechanisms. However, these therapies frequently fail to provide complete relief or are poorly tolerated by many patients (15).

Similarly, the European Society of Human Reproduction and Embryology (ESHRE) 2022 guidelines support the use of NSAIDs as initial therapy but acknowledge that the recommendation is based on low-certainty evidence from limited RCTs. Hormonal treatments particularly progestins and COCs are better supported by clinical data and are recommended for long-term symptom control. Yet, even these have limitations in efficacy and tolerability (16). NICE guideline (2024) recommends offering a short trial (up to 3 months) of NSAIDs or paracetamol for endometriosis-related pain. Although the recommendation does not specify the evidence quality in the guideline text, the underlying evidence review indicates that the certainty of benefit from NSAIDs is low, based on few and underpowered studies. It also recommends offering hormonal treatment to individuals with suspected or confirmed endometriosis (17).

While effective for many, the guideline notes that some people may not respond, tolerate, or wish to take these treatments, in which case referral for further assessment, including surgical options, is advised. Cochrane evidence reports no high-quality benefit of hormonal therapy over placebo for pain relief (18). Despite clinical guidelines, significant treatment attrition due to suboptimal therapeutic response, adverse effects, contraindications, or non-hormonal preferences occurs, reflecting symptom-suppressive approaches over pathogenesis-targeting therapies, while diagnostic delays (7-12 years) persist owing to heterogeneous presentation and lack of definitive non-invasive diagnostics**.** (3). Following diagnosis, personalized therapeutic options are often inadequate, necessitating urgent development of safe, mechanism-based adjunct therapies particularly non-hormonal, well-tolerated, and accessible modalities to complement current management

Oxidative stress in endometriosis pathogenesis: Emerging evidence implicates oxidative stress as a central mechanism in endometriosis pathogenesis (19). Women with the condition exhibit 2–3-fold elevations in reactive oxygen species (ROS) within peritoneal fluid and diminished endogenous antioxidant activity, including reduced superoxide dismutase (SOD) and catalase levels. These biochemical disturbances correlate with increased lesion severity and pain intensity (20). The antioxidant defense system particularly enzymes like SOD and glutathione peroxidase plays a vital role in mitigating ROS. In endometriosis, these systems are impaired, leading to sustained inflammation and tissue damage. This has generated interest in antioxidant supplementation as a therapeutic strategy (21).

Evidence on antioxidant therapy: Several antioxidant agents have demonstrated therapeutic potential as adjuncts in preclinical and clinical studies, with human trial data summarized in table 1. The current evidence base is characterized by variability in outcomes, reflecting differences in study design, dosage, treatment duration, and endpoints.

- **Vitamin E and C**: Reduce pelvic pain in small clinical trials, likely through synergistic reduction of lipid peroxidation and oxidative markers, such as malondialdehyde (MDA), and improvement of antioxidant defenses (6, 7).
- **N-acetylcysteine**: Decreases lesion size and pain in studies by enhancing glutathione and reducing ROS (8), larger clinical trials are needed to confirm these findings.
- **Curcumin**: Demonstrates significant anti-inflammatory and antioxidant properties by inhibiting NF-κB signaling and reducing lesion growth in animal models. However, a recent RCT found it no more effective than placebo for pain relief, indicating a need for more research to reconcile preclinical and clinical results (22).
- **Vitamin D**: Modulates oxidative stress and immune response by increasing the expression of antioxidant enzymes and regulating cytokines like IL-10 and TNF-α. As shown in table 1, clinical results for pain reduction are mixed, and its impact on lesion regression remains unclear
- **Resveratrol**: Inhibits inflammatory and angiogenic pathways, including the suppression of VEGF and IL-6, and reduces lesion growth in preclinical models (8). However, a single RCT found no significant effect on dysmenorrhea (table 1), highlighting a gap between animal and human findings.
- **Melatonin**: Particularly promising for its dual antioxidant and analgesic roles. It has shown lesion volume reduction in animal models (23, 24) by modulating oxidative stress and suppressing inflammatory mediators (e.g., VEGF, IL-6, MMPs). Its mechanisms include restoring antioxidant balance (reducing MDA and increasing SOD/CAT, inhibiting NF-κB/NLRP3 inflammasome pathways, and modulating pain perception through MT1/MT2 receptors) (25). A recent systematic review and meta-analysis reported a mean reduction of 1.89 points on the visual analog scale (VAS) for dysmenorrhea with melatonin therapy (Esmaeilzadeh, et al. 2025. DOI:10.1186/s12958-025-01485-x). Evidence on lesion regression remains limited and inconclusive, with one small RCT showing no

significant effect. Despite this, melatonin's multifaceted actions and favorable safety profile make it a viable adjunct therapy, particularly for patients seeking non-hormonal options (26).

Variability in clinical outcomes reflects differences in dosage, treatment duration, and endpoints. Among all agents, melatonin's safety profile and non-hormonal mechanism make it a promising adjunct pending further validation. Antioxidants should currently be considered complementary to standard care until high-quality evidence from larger, well-designed trials confirms their effectiveness for both symptom relief and disease modification.

Policy implications: The potential role of antioxidants in endometriosis management particularly agents like melatonin and curcumin has several policy-relevant implications, though current evidence is of low certainty and requires cautious interpretation:

Patient-centered care: Surveys indicate most patients prefer non-hormonal options due to dissatisfaction with hormonal side effects (27).

Cost-effectiveness: While robust health economic analyses are lacking, antioxidants' low cost and over-the-counter (OTC) availability suggest potential to reduce dependence on higher-cost interventions pending confirmation of clinical efficacy in future trials

Health equity: Accessibility in low-resource settings could improve care equity.

Table 1. Evidence profile for antioxidant therapies in endometriosis pain

Antioxidant	Quantity of Evidence (Total N)	Consistency of Results	Conclusion on Efficacy	Recommended for Policy Consideration?
Melatonin	5 RCTs (N=~209)	Mostly Consistent (4/5 trials positive)	Likely Efficacious for pain reduction at doses of 5-10mg/day.	Yes. Strong safety profile and multiple positive trials support inclusion in clinical guidance as an adjunct.
Vitamin C+E	4 RCTs (N=~279)	Mostly Consistent (3/4 trials positive)	Likely Efficacious for overall pain reduction.	Yes. Low cost and wide availability make it a viable option for adjunctive care, especially in resource-limited settings.
Vitamin D	2 RCTs (N=~98)	Inconsistent (1 positive, 1 null)	Inconclusive.	No. Conflicting evidence does not currently support a recommendation. More research is needed.
Curcumin	1 RCT (N=68)	N/A (Single study)	No significant effect demonstrated.	No. A single high-quality trial found it no better than control. Not currently supported.
Resveratrol	1 RCT (N=44)	N/A (Single study)	No significant effect demonstrated.	No. Limited and negative evidence does not support recommendation
Garlic Powder	1 RCT (N=120)	N/A (Single study)	Preliminary positive effect.	For Research. Promising result must be replicated before clinical or policy consideration.
Silymarin	1 RCT (N=70)	N/A (Single study)	Preliminary positive effect.	For Research. Promising result must be replicated before clinical or policy consideration.

Evidence gaps: Existing evidence is of low certainty (GRADE), primarily from small, short-term studies with heterogeneous endpoints; well-powered randomized controlled trials are needed to inform clinical guidelines and regulatory policy.

Personalized medicine: Antioxidant therapies represent a promising adjunct for personalized management, particularly when biomarker-guided, but require further clinical validation

Recommendations:

- **Support Clinical Trials**: Prioritize funding for large, well-designed randomized controlled trials to evaluate the efficacy and safety of melatonin, curcumin, vitamin D, and other antioxidants for both pain relief and lesion size reduction in endometriosis.
- **Update Guideline**: Consider provisional inclusion of antioxidants as adjunct therapies within multidisciplinary frameworks, contingent on supportive clinical trial evidence.
- **Train Clinicians**: Implement continuing medical education (CME) programs on current evidence, limitations, and appropriate application of antioxidant therapy.

Patient awareness and shared decision-making: Implement public education campaigns and clinical tools educating patients on non-hormonal adjunct options, emphasizing evidence-based use and realistic expectations.

- **Biomarker-guided research and care**: Support the development of diagnostic tools and predictive biomarkers (e.g., oxidative stress profiles) to help identify subgroups of patients who may benefit most from antioxidant-based interventions

Conclusion: Antioxidant therapy particularly melatonin offers a promising, low-risk, and accessible adjunct for managing endometriosis-related pain. While current evidence supports its use for symptom relief, inconsistent findings on lesion regression and the lack of guideline inclusion necessitate further study. Policy interventions should aim to close this evidence gap by supporting research, clinical integration, and patient education. A paradigm shift toward mechanism-targeted, personalized, and multidisciplinary care will be essential to improving outcomes for women living with endometriosis.

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Authors' contribution: PM. designed the study and wrote the manuscript. MAD performed experiments and edited the manuscript. SE. supervised the research and edited the manuscript. All authors approved the final version.

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