ISSN (Online) 3134-8823

Journal of Advanced Biological Sciences

Received: December 27, 2025 | Accepted: April 14, 2026 | Published: June 30, 2026
Volume 03, Issue 01, Pages 25-27

DOI https://doi.org/10.66590/jabs2026030105

Review Article

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Modifiable Behavioral and Psychosocial Determinants of Primary Female Infertility: A Mechanistic Narrative Review

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How to Cite the Article:
Ahmad, Hamdan Siddig Sirag *et al.* "Modifiable Behavioral and Psychosocial Determinants of Primary Female Infertility: A Mechanistic Narrative Review." *Journal of Advanced Biological Sciences*, vol. 03, no. 01, June 2026, pp. 25-27. https://doi.org/10.66590/jabs2026030105

Abstract | Primary female infertility is a complex, multifactorial reproductive disorder influenced by unmodifiable organic etiologies as well as modifiable behavioral and psychosocial factors. This narrative review synthesizes current molecular, cellular and endocrine evidence linking body composition, physical activity, dietary patterns and psychological distress to primary female reproductive dysfunction. We highlight specific physiological pathways, including hypothalamic Gonadotropin-Releasing Hormone (GnRH) pulsatility, the hypothalamic-pituitary-adrenal (HPA) axis, follicular microenvironment oxidative stress and peripheral insulin signaling. Furthermore, actionable clinical guidelines for preconception lifestyle modifications are provided alongside prioritized future research avenues. Routine evaluation of modifiable lifestyle parameters represents an essential component of comprehensive reproductive healthcare.

Key Words Primary Female Infertility, Lifestyle Factors, Body Composition, Physical Activity, Dietary Patterns, Psychological Distress, Reproductive Dysfunction

INTRODUCTION

Infertility affects an estimated 10–15% of reproductive-aged couples worldwide, presenting a significant clinical and public health challenge [1]. While primary female infertility is frequently attributed to anatomical anomalies, tubal pathology, endometriosis, or premature ovarian insufficiency, an increasing body of biological evidence demonstrates that modifiable behavioral and psychosocial factors significantly alter female reproductive capacity [2,3]. Endocrine signaling governing ovulation, follicular maturation and endometrial receptivity depend heavily on metabolic homeostatic balance and neuroendocrine regulation [4].

Key modifiable determinants including excess adiposity, physical inactivity or extreme exercise, pro-inflammatory dietary patterns and chronic psychological distress disrupt the delicate cross-talk along the Hypothalamic-Pituitary-Ovarian (HPO) axis [5,6]. Elucidating these mechanistic pathways is crucial for developing targeted non-pharmacological interventions, optimizing natural fecundability and enhancing outcomes in Assisted Reproductive Technology (ART) protocols.

Pathophysiological Mechanisms of Modifiable Determinants

Adiposity, Adipokines and Metabolic Endocrine Disruption: Both elevated Body Mass Index (BMI ≥ 25.0 kg/m^2) and energy deficient states (BMI < 18.5 kg/m^2) profoundly impact ovarian physiology [6,7]. In hypertrophic visceral adipose tissue, altered adipokine secretion occurs: elevated leptin levels paired with reduced adiponectin concentration promote a baseline pro-inflammatory state [8]. Compensatory hyperinsulinemia driven by insulin resistance acts synergistically with Luteinizing Hormone (LH) on ovarian theca cells, upregulating cytochrome P450c17α activity and driving excessive intraovarian androgen production [9]. Hyperandrogenism leads to premature follicular atresia and chronic anovulation, as observed in Polycystic Ovary Syndrome (PCOS). Conversely, low energy availability suppresses pulsatile GnRH release, resulting in hypogonadotropic hypogonadism [7].

Physical Activity Spectrum and Systemic Perfusion

Physical activity exhibits a parabolic, U-shaped association with female fecundability [10,11]. Sedentary behavior promotes peripheral insulin resistance, upregulates systemic inflammatory markers (such as TNF-α and IL-6) and alters pelvic microvascular hemodynamics [10]. Moderate aerobic and resistance exercise enhances GLUT4 glucose transporter expression, improves insulin sensitivity and restores regular ovulatory function [11]. However, exhaustive high-intensity exercise without adequate caloric compensation triggers relative energy deficiency, elevating basal glucocorticoid levels and blunting the pre-ovulatory LH surge [10].

Dietary Composition and Follicular Microenvironment Oxidative Stress

Dietary composition directly conditions the microenvironment within the pre-ovulatory follicle [5,12]. High intake of refined carbohydrates with elevated glycemic index causes rapid postprandial glucose fluctuations, compounding hyperinsulinemia and oxidative stress in cumulus-oocyte complexes [5]. Diets rich in industrial trans-fatty acids and saturated fats accelerate Reactive Oxygen Species (ROS) production, compromising oocyte meiotic spindle formation and mitochondrial function [6]. Conversely, Mediterranean-style dietary patterns high in omega-3 polyunsaturated fatty acids (n-3 PUFAs), folate and micronutrient antioxidants protect against cellular oxidative damage and improve implantation rates [12,13].

Psychosocial Stress and HPA-HPO Axis Cross-Talk

Chronic psychological distress engages the Hypothalamic-Pituitary-Adrenal (HPA) axis, stimulating Corticotropin-Releasing Hormone (CRH) and systemic glucocorticoid secretion [14,15]. Cortisol directly suppresses hypothalamic GnRH neuronal firing and blunts pituitary responsiveness to GnRH, leading to deficient LH and FSH secretion [14]. Concurrently, sympathetic nervous system hyperactivation elevates circulating catecholamines, inducing vasoconstriction in uterine and ovarian arteries, thereby compromising endometrial thickness and nutrient transport to developing follicles [15,16].

Table 1: Biological Pathways Linking Modifiable Determinants to Female Reproductive Dysfunction

Modifiable Determinant	Primary Biological Pathway	Impact on Reproductive Physiology
Excess Adiposity (BMI ≥ 25)	Hyperinsulinemia & Adipokine Dysregulation	Increases theca androgen synthesis; promotes follicular arrest and anovulation.
Underweight (BMI < 18.5)	Energy Deficiency & Hypothalamic Blunting	Suppresses GnRH pulsatility, leading to hypogonadotropic hypogonadism.
Sedentary Behavior	Insulin Resistance & Systemic Inflammation	Elevates TNF-α/IL-6; impairs pelvic organ vascular perfusion.
Strenuous Exercise	HPA Axis Activation & Negative Energy Balance	Elevates baseline cortisol; induces luteal phase defects or amenorrhea.
High Glycemic Diet	Postprandial Glucose Spikes & Hyperinsulinemia	Exacerbates intraovarian hyperandrogenism and oxidative stress.
Trans-Fatty Acids	Mitochondrial Dysfunction & ROS Accumulation	Impairs cumulus-oocyte complex quality and meiotic spindle integrity.
Psychosocial Stress	HPA Axis Hyperactivation & Sympathetic Tone	Suppresses GnRH/LH pulsatility; increases uterine vascular resistance.

Table 2: Preconception Lifestyle Interventions and Targeted Clinical Outcomes

Lifestyle Domain	Targeted Intervention Protocol	Primary Biological Outcome	Clinical Recommendation
Weight Management	5–10% weight loss in overweight/obese patients	Normalizes insulin sensitivity and LH/FSH ratio	First-line therapy prior to ovulation induction
Physical Activity	≥ 150 min/week moderate aerobic + resistance training	Reduces systemic inflammation and improves GLUT4 expression	Avoid exhaustive endurance training (> 4 hr/week intense)
Dietary Modification	Mediterranean pattern rich in n-3 PUFAs and antioxidants	Reduces follicular fluid oxidative stress	Replace trans/saturated fats with monounsaturated/omega-3 fats
Stress Reduction	Cognitive Behavioral Therapy (CBT), mindfulness, yoga	Decreases salivary cortisol and normalizes GnRH pulsatility	Integrate psychological screening into fertility clinics

Table 3: Diagnostic Screening Tools for Modifiable Behavioral and Psychosocial Determinants

Clinical Domain	Recommended Assessment / Instrument	Clinical Cut-Off / Target Parameter
Body Composition	BMI Measurement & Waist-to-Hip Ratio (WHR)	Target BMI: 18.5–24.9 kg/m^2; WHR < 0.80
Physical Activity	International Physical Activity Questionnaire (IPAQ)	Target: 600–1500 MET-minutes/week
Dietary Quality	Food Frequency Questionnaire (FFQ) / Diet History	High adherence to Mediterranean Diet Score (MDS ≥ 6)
Psychosocial Stress	Perceived Stress Scale (PSS-10) / DASS-21	Identify moderate-to-severe anxiety/stress (PSS>13)

Table 4: Priority Directions for Future Biological and Clinical Research

Research Domain	Current Knowledge Gap	Proposed Research Direction
Epigenetics	Transgenerational inheritance of lifestyle-induced epigenetic marks	Investigate microRNA and DNA methylation changes in oocytes and granulosa cells.
Microbiome	Role of gut/vaginal microbiota in reproductive inflammation	Assess endo-microbiome influence on endometrial receptivity and PCOS metabolism.
Digital Health	Efficacy of mobile lifestyle coaching on ART clinical pregnancy rates	Conduct large multi-center randomized controlled trials (RCTs) utilizing wearable tracking.

Clinical Evidence, Screening and Preconception Guidance

Targeting modifiable lifestyle determinants provides a highly effective, cost-efficient strategy for optimizing female fertility prior to or alongside clinical assisted reproduction [2,3]. Evidence-based interventions and their biological targets are synthesized in Table 1-4.

CONCLUSIONS

Modifiable behavioral and psychosocial factors exert profound, biological control over primary female fertility. Excess adiposity, sedentary habits or extreme physical strain, poor dietary quality and chronic psychological stress intersect at the cellular and endocrine levels, disrupting HPO axis signaling, increasing oxidative stress and compromising endometrial receptivity. Integrating routine lifestyle screening and structured non-pharmacological interventions into preconception care represents a powerful, high-yield avenue to optimize reproductive outcomes.

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