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The Gut-Reproductive Axis and Female Fertility: An Overview

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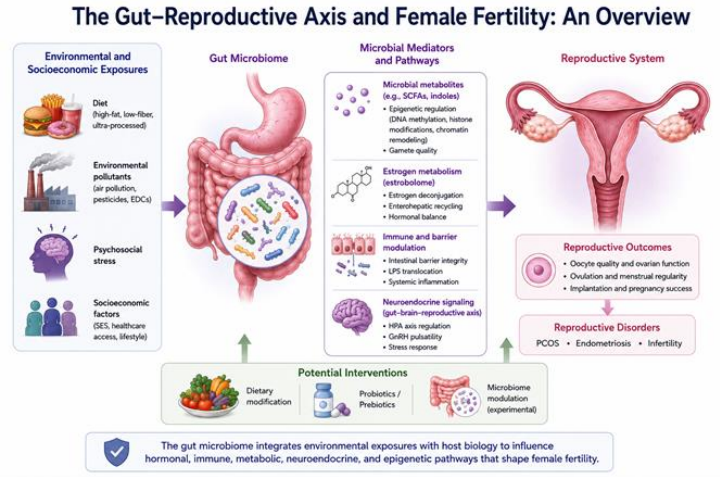
Abstract

Female fertility is now understood to be a systemic phenomenon, where hormone release, immunity, metabolism, environmental factors, and neuroendocrine control play crucial roles. Recent data indicate that the gut microbiome plays an important role as a regulator of female reproduction through the gut-reproductive axis involving hormonal signals, immunity, metabolism, and epigenetics. Environmental and social factors like nutrition, stress, and pollutants can alter the gut microbiome and possibly cause reproduction disorders. The products of microbial metabolism, such as short-chain fatty acids, might affect estrogen biosynthesis, inflammation processes, and gamete formation through epigenetic processes. The connection between dysbiosis and disorders like PCOS, endometriosis, and infertility has been observed; however, the causal link is yet to be proven.

Graphical Abstract



Note: This figure was generated using ChatGPT (OpenAI, GPT-5.3) via text-to-image conversion and subsequently refined through manual editing for clarity and presentation.

Keywords: gut microbiome; female fertility; gut–reproductive axis; epigenetics; short-chain fatty acids; dysbiosis; PCOS; endometriosis; reproductive health; environmental exposures; estrobolome; neuroendocrine signaling

Gut Microbiome and Female Reproductive Health

Fertility in females is increasingly being viewed as a systems-based phenotype mediated through complex endocrine, immune, metabolic, environmental, and neuroendocrine interactions, rather than solely through the functioning of reproductive organs [1-4]. Within this framework, the gut microbiota has emerged as a key regulator of host physiological functions. Studies in germ-free animal models have demonstrated alterations in hypothalamic-pituitary-gonadal (HPG) axis signaling, hormone regulation, and reproductive function, thereby supporting the existence of a gut-reproductive axis [5-7]. Environmental and socioeconomic factors critically modulate this axis upstream through their influence on gut microbial composition [8,9]. Diet remains one of the strongest determinants of microbial ecology. Diets high in fat, low in fiber, and rich in ultra-processed foods have been associated with reduced microbial diversity and depletion of short-chain fatty acid (SCFA)-producing bacteria, whereas fiber-rich diets support a metabolically favorable microbial environment [10,11]. Exposure to environmental toxicants, including air pollutants, pesticides, and endocrine-disrupting chemicals such as bisphenol A and phthalates, may also alter gut microbial composition [12,13]. Socioeconomic conditions can influence this axis at multiple levels by affecting dietary quality, environmental exposure burden,

access to health care, and chronic psychological stress [14,15].

Accumulating evidence suggests that microbial metabolites may mediate environmental influences on reproduction through epigenetic mechanisms [16,17]. SCFAs and other microbiota-derived metabolites can influence histone acetylation, DNA methylation, chromatin remodeling, and other chromatin regulatory pathways that are important for metabolism, ovarian function, and gamete quality [18-21]. In addition, emerging evidence indicates that environmentally induced alterations in microbiota composition may contribute to epigenetic modifications in gametes [22-24]. Such alterations have been hypothesized to contribute to reduced fertility, supported in part by the identification of epigenetic signatures associated with poor-quality gametes [25,26]. Histone modifications and chromatin remodeling are known to influence fertility; for example, abnormal accumulation of histone H3 lysine 4 dimethylation (H3K4me2) in sperm has been associated with impaired sperm quality and developmental defects [27,28]. Similarly, dynamic changes in DNA methylation during oocyte maturation are important determinants of oocyte quality [29,30]. The gut microbiota may influence reproductive physiology through both endocrine and immunological pathways. One important mechanism involves estrogen metabolism mediated by the estrobolome, in which bacterial β-glucuronidase activity promotes estrogen deconjugation and enterohepatic recirculation, thereby influencing systemic estrogen availability [31,32]. Several observational studies have reported associations between gut microbial diversity and circulating estrogen levels across different reproductive stages, including menopause [33,34]. Concurrently, disruption of gut barrier integrity during dysbiosis may permit translocation of microbial products such as lipopolysaccharide (LPS), contributing to systemic low-grade inflammation that has been associated with disorders including polycystic ovary syndrome (PCOS) [35,36].

Gut-derived metabolites, particularly SCFAs, add another dimension to microbiome-reproductive communication. Preclinical studies suggest that SCFAs modulate immune signaling, metabolism, and epigenetic regulation, and that diet-associated dysbiosis may adversely affect folliculogenesis and ovarian physiology [37-39]. The gut microbiome may also indirectly influence ovarian aging through modulation of oxidative stress and mitochondrial dysfunction, both of which are established contributors to reproductive senescence [40,41]. In addition to endocrine and immunological pathways, communication between the microbiota and the reproductive system may occur through neuroendocrine mechanisms involving the gut-brain-reproductive axis [42,43]. Germ-free animals exhibit exaggerated hypothalamic-pituitary-adrenal (HPA) axis responses to stress, which can be normalized following microbial colonization [44,45]. Stress-mediated suppression of gonadotropin-releasing hormone (GnRH) pulsatility may contribute to anovulation, while microbiota-derived metabolites may influence tryptophan metabolism and downstream neuroendocrine signaling [46,47].

These interactions are increasingly reflected in clinical associations between gut microbiome alterations and reproductive disorders. Altered gut microbial composition has been reported in patients with PCOS, endometriosis, and idiopathic infertility [48-51]. Reduced microbial diversity and compositional shifts have been associated with insulin resistance, hyperandrogenism, and inflammation in PCOS; however, no reproducible disease-specific microbial signature has yet been established [52,53]. Similar associations have been described in endometriosis and idiopathic infertility, although findings remain inconsistent across studies [54,55]. In light of these emerging connections, therapeutic modulation of the gut microbiome has gained attention as a potential strategy in reproductive medicine, although current applications remain largely experimental. Dietary interventions emphasizing increased fiber intake, along with probiotics and prebiotics, have been shown to improve gut microbial diversity and confer metabolic and anti-inflammatory benefits in PCOS [56,57]. However, their effects on reproductive outcomes remain insufficiently characterized.

In summary, the gut-reproductive axis provides an integrative framework linking microbial ecology, environmental exposures, endocrine biology, immunology, epigenetics, and reproductive physiology. Although substantial biological plausibility has emerged from preclinical and observational studies, much of the human evidence remains correlational. Further mechanistic and longitudinal studies are therefore required to establish causality and evaluate the translational potential of microbiome-targeted interventions in reproductive health.

Declarations

Conflict of Interest

The author does have anything to declare.

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