Women's Health, Hormones, and the Microbiome

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The female body has long been romanticized as mysterious, with many aspects of women's health remaining enigmatic today. Why are women more likely than men to develop osteoarthritis, autoimmune disorders, heart disease, certain cancers, and mental health conditions such as anxiety and depression?[1] Why do women and men often experience different health outcomes and lifespans?

Researchers have only recently begun to explore these questions and study the differences between men's health and women's health. Clinical findings that may help partly explain these disparities have focused on hormones and the female microbiome, both of which play distinct roles in regulating immune function.

Different health experiences between the sexes

Women and men experience significant health differences due to biological, genetic, hormonal, and lifestyle factors. Physically, women have smaller hearts and narrower blood vessels than men[2]; tighter esophageal sphincters, with less stomach acid and slower stomach emptying; and longer colons (nearly 10 centimeters longer than men's), with the added complexity of sharing space with major reproductive organs.[3]

These structural differences mean women and men sometimes experience certain symptoms and conditions differently, yet they are often treated with the same healthcare interventions. For example, for cardiovascular disease, men typically develop more plaque buildup in the larger arteries, while women tend to develop plaque in the microvasculature of the heart.[2] This distinctive difference should be considered when choosing the best therapeutic interventions for women (and patients assigned female at birth).

Genetics greatly influences both biological sexes in terms of overall health and susceptibility to certain health disorders. While the Y chromosome contains a small number of genes, such as the *SRY* gene responsible for male gonad development, the X chromosome contains over 1000 genes, many of which are related to immune function.[4]

Women's immune systems, in particular humoral immunity, are more robust than men's to ensure their ability to reproduce. Elevated antibodies allow an adaptive advantage for reproduction, as well as the transfer of protective antibodies to offspring.[5] Although this protective mechanism allows women to clear pathogens faster, it leads to a higher incidence of inflammatory diseases. Consequently, 80% of patients with autoimmune diseases are female.[6]

Hormones and the microbiome are both significant factors when it comes to understanding women's susceptibility to autoimmune and other disorders.

Health conditions with a higher prevalence among women

Connective tissue diseases (autoimmune)	Sjogren syndrome Systemic lupus erythematosus Scleroderma Rheumatoid arthritis Osteoarthritis
Thyroid conditions	Hypothyroid Hyperthyroid Autoimmune thyroiditis: Hashimoto disease and Grave disease
Skin conditions	Eczema Acne Alopecia Rosacea Melasma
Cardiovascular conditions	Coronary artery disease (postmenopause) Microvascular artery plaque Coronary spasm Coronary dissection Broken heart syndrome
Gastrointestinal conditions	Irritable bowel syndrome Gallstones Constipation Gastroparesis Celiac disease (autoimmune)
Neurological conditions	Migraine Multiple sclerosis (autoimmune) Alzheimer disease Stroke

Hormones and immune function

Sex hormones are directly responsible for some of the differences in immune function between males and females. High levels of estrogen or low levels of progesterone, for example, may contribute to immune dysregulation in women.

Estradiol, the primary circulating estrogen in women, contributes to many immune-stimulating activities that depend on the concentration of circulating estradiol as well as the density and types of estrogen receptors present (eg, ERα is highly expressed by T cells; ERβ is highly expressed by B cells).[6]

Low levels of estradiol influence monocytes and macrophages by boosting proinflammatory cytokines and stimulating T_H1-type and cell-mediated responses, which aid in defending against intracellular pathogens. In contrast, higher levels of estradiol decrease these cytokines and support T_H2-type responses and humoral immunity typically associated with allergies.[6] Estradiol also increases the number of circulating neutrophils and can differentiate monocytes into inflammatory dendritic cells. These effects increase interferon α and proinflammatory cytokine expression, toll-like receptor (TLR7 and TLR9) signaling, and internalization and presentation of antigens to naive T cells, which most likely contribute to the greater type I interferon activity seen in women versus men.[6]

Progesterone, found in fluctuating levels in menstruating women and in high levels in pregnant women, has broad anti-inflammatory effects.[6] It has been shown to support immune modulation and enhance immune tolerance by lowering circulating cytokines and increasing regulatory T cells.[7] These changes are demonstrated clinically in women with autoimmune conditions who experience a drastic decrease in symptoms when they become pregnant. Progesterone also enhances smooth muscle relaxation and supports the dilation of blood vessels, contributing to lower blood pressure through its influence on calcium channels.[8] Its balancing effects—on both estrogen levels and immune function—are critical for women when it comes to immune regulation.

Androgens such as dihydrotestosterone (DHT) and testosterone, found in higher concentrations in postpubertal men than in women, have more immune-suppressive activities in general compared to estrogen. DHT and Testosterone increase IL-10 and transforming growth factor-β (TGFβ) synthesis enhancing anti-inflammatory responses through androgen receptor signaling. These androgens are also responsible for lowering pro-inflammatory responses by reducing extracellular signal-regulated kinases and leukotrienes in neutrophils.[6] Because of the immune-suppressive actions of androgens, men have historically had lower incidences of inflammatory-mediated immune conditions.

The microbiome

Whether male or female, the human body houses trillions of microbes, including bacteria, fungi, viruses, and archaea. These microbes exist symbiotically and play a vital role in many host biological functions, such as immune priming and tolerance, nutrient synthesis, metabolism control, inflammation modulation, and hormonal and neurotransmitter regulation. The diverse and abundant microbes that reside in the gut help our immune systems appropriately identify and target foreign invaders, elicit an immune response, and bring our immune systems back to baseline. Thus, anything that disturbs or alters this composition can affect immune function.

Although we know that diet is perhaps one of the most significant factors affecting gut microbiota composition—followed by stress and environmental exposures—differences between biological sexes are also being explored as potential factors.

Microbial differences between sexes. Studies examining sex-dependent differences in the gut microbiome have reported conflicting results. However, most demonstrated that a woman's gut microbiota composition has lower *Bacteroides* abundance and higher α diversity, a measure of diversity within an individual sample, than men's.[1] Influencing factors included body mass index, species level versus genus level of microbes, and host health, with women and men with enteric infections exhibiting a greater difference in microbiome composition than healthy individuals.[9] Interestingly, the ratio of bacteria to human cells is higher in women, at 2.2:1 than in men, at 1.3:1.[9,10]

The microbiota is similar among males and females in early life, with factors such as birth type (vaginal versus cesarean), feeding method (breastfed versus bottle-fed), and diet being the primary influencers during a child's early years. Sex differences in the gut microbiota do not appear until puberty.[9]

Changes in gut composition during puberty highlight the role sex hormones play in shaping gut differences between women and men. Microbes of the same species can produce different metabolites in women and men because the microbes interact differently with different sex hormones.[11] Because sex hormones influence the composition of the gut microbiota, microbial communities of men and women differ after puberty. The microbiome also develops alongside the immune and nervous systems, leading to differences in immune and neuroinflammatory pathway development in women and men.[11]

Gut dysbiosis and functional digestive disorders. It has been well established that differences in the gut microbiota among women and men affect sex-specific immunity changes and drive a number of chronic diseases, such as gastrointestinal, inflammatory, metabolic, neurological, cardiovascular, and respiratory illnesses.[12]

Emerging evidence shows the interplay between sex hormones and microbial composition, as seen in the microbiota's role in hormone circulation, metabolism, and excretion. When not functioning optimally, this gut-hormone axis may contribute to functional gastrointestinal disorders and the various gut symptoms each sex experiences.[10]

When the microbiome is out of balance—a state known as dysbiosis—overgrown microbes and their metabolites cause local inflammation of the intestinal lining. Through translocation, this dysbiosis can lead to immune dysregulation and body-wide ailments, as well as hormonal imbalance. Hormonal imbalance can also lead to dysbiosis. Thus, studies

have implied sex hormones affect the pathogenesis of many diseases and the development of gut symptoms. For example, women are twice as likely as men to suffer from irritable bowel syndrome, which affects the small bowel and colon. Additionally, symptoms of irritable bowel syndrome can be linked to a woman's menstrual cycle, often becoming more severe at the beginning of their period as hormones fluctuate.[3]

Gut microbiome and hormones. There is a bidirectional effect between sex hormones and the microbiome. Estrogen (and, to a lesser degree, progesterone) can influence microbial diversity and abundance, while microbes in the gut can regulate systemic steroid hormone levels.

Estrogen

Although estrogen's primary role is related to reproductive functioning, estrogen and other sex steroids can act on nonreproductive systems and functions, including the immune, central nervous, cardiovascular, digestive, and skeletal systems, as well as cells in the liver, skin, and kidneys.[13] As noted earlier, estrogen plays a pivotal role in stimulating and regulating immune responses and directly impacts both the innate and adaptive immune systems.[13]

Besides directly stimulating immune function, estrogen has been known to support the growth of beneficial flora, including *Lactobacillus* and *Bifidobacterium* species, which support gut integrity and produce beneficial metabolites. It does this through its ability to affect bile acid composition. Bile acid is needed to support the metabolism of fats. However, it also plays a vital role in feeding beneficial flora while acting as an antimicrobial to prevent the overgrowth of harmful organisms.

Estriol and estradiol also inhibit pathogenic microbe growth and virulence by disturbing quorum sensing.[1] Estrogen and progesterone can upregulate tight junction proteins, modifying gut epithelial barrier integrity. Estradiol also helps protect mucus-producing intestinal epithelial cells against oxidative injury.[14] Murine studies have further demonstrated that women are more resistant to gut injury than are men.[1]

Estrogen also enhances insulin sensitivity and regulates lipid metabolism—activities that support a healthy metabolic state.[15] Improved insulin sensitivity and lipid profiles can promote a gut environment that supports diverse and beneficial microbial communities. Additionally, estrogen's anti-inflammatory effects promote a healthy and diverse microbiome, supporting overall health.

Estrogen balance. Women have notably higher estrogen levels than men, another reason for women's more robust immune responses. As referred above, estrogen provides many health benefits to the host, however when estrogen levels become dysregulated this can lead to undesirable systemic effects. Out-of-balance estrogen levels can contribute to conditions such as autoimmune disorders. β-Estradiol, for instance, can influence dendritic cells to produce interleukin 12 and interferon γ.[16] These proinflammatory cytokines can lead to a compromised gut lining, causing gut microbiota and their metabolites to migrate systemically and further promote body-wide inflammation and immune dysregulation.

The estrobolome. Just as estrogen influences microbial composition, the gut microbiome can influence estrogen through the estrobolome. The estrobolome is a specific collection of bacteria from the enteric microbiome whose products are capable of influencing estrogens. It metabolizes and modulates the body's circulating nonovarian estrogen, which in turn affects weight, mood, libido, and lifetime accumulative exposure to estrogens.[16]

In the final of the 3 phases of estrogen detoxification, the liver and intestines bind toxins and steroid hormones to glucuronic acid, allowing toxins to be eliminated in the stool. β-Glucuronidase, an enzyme produced by the estrobolome, can deconjugate estrogens and other compounds in bile, preventing excretion and enhancing reabsorption, which increases overall systemic levels of these metabolites.[1,16] When the microbiome is in homeostasis, this mechanism is protective, ensuring that appropriate amounts of circulating estrogens are present.

The estrobolome and dysbiosis. When a dysbiotic state is caused by an increased Bacillota:Bacteroidota (formerly Firmicutes:Bacteroidetes) ratio[17] or elevated levels of microbes such as Clostridia taxa and some Ruminococcaceae[11] that produce β-glucuronidase, it increases the toxic burden on the body caused by reabsorbed endocrine-disrupting chemicals and raises systemic estrogen, leading to an estrogen-dominant state. Deconjugated estrogens circulate and bind to estrogen receptors (ERα and ERβ) in reproductive organs but also affect the immune, skeletal, cardiovascular, and central nervous systems.[10] Estrogen dominance through mechanisms of compromised gut permeability and immune dysfunction is associated with diseases such as endometrial hyperplasia, endometrial cancer, breast cancer, endometriosis, and uterine fibroids.[17]

When dysbiosis results in a decrease in gut microbiome abundance, the opposite effect may ensue. A drop in β-glucuronidase slows down deconjugation, leading to a reduction in circulating estrogens. A hypoestrogenic state is associated with obesity and metabolic syndrome as well as polycystic ovarian syndrome, cardiovascular disease, increased susceptibility to osteopenia and osteoporosis, and impaired cognition.[17,18] Thus, the gut microbiome regulates estrogen metabolism, playing a significant role in estrogen-related disorders.

Life stages and the microbiome

Women go through stages of drastic hormonal changes throughout life: puberty, menopause, and—if they bear children—pregnancy and postpartum. These sharp changes in levels of estrogen and other hormones contribute to psychological changes and physical changes, such as those seen in immune function, and can increase risks for certain conditions.

Table 1 shows a summary of changes that occur in the microbiome at different stages in a woman's life and in response to specific conditions.

Puberty. Puberty marks a time of tremendous change for women as sex hormone levels rise, stimulating physical

Table 1. Summary of gut microbiota in women.[11]

Healthy female	Decreased: *Bacteroides* abundance with increased diversity than in men
	Increased: *Lactobacillus, Bifidobacterium* and *Parabacteroides* than in men
Menstruation	Decreased: *Bacteroidota, Butyricicoccus, Extibacter, Megasphaera, Parabacteroides*
Pregnancy	Increased: *Actionbacteria, Proteobacteria, Akkermansia, Bifidobacterium, Bacillota*
	Decreased: Short chain fatty acids producers
Polycystic ovarian syndrome	Increased: *Phocaeicola vulgatus, Bacillota, Streptococcus, Esherichia/Shigella*
	Decreased: *Tenericutes, Akkermansia, Oscillospuraceae*
Menopause	Increased: *Bacillota, Roseburia, Lachnospira, Bacteroidota*
	Decreased: *Bilophila, Prevotella, Parabacteroides*
Breast cancer	Increased: *Eubacteriales, Bacillus, Enterobacteriaceae, Staphylococcus*
Cervical cancer	Increased: *Proteobacteria, Prevotella, Poryphromonas, Dialister*
	Decreased: *Bacteroides, Alistipes, Lachnospiraceae*
Ovarian cancer	Increased: *Prevotella, Coriobacteriaceae, Bifdobacterium*

developmental maturation and the commencement of menstruation. Preteens and teenagers going through puberty may start to experience more anxiety or depression as these hormonal changes can bring about uncertainty, vulnerability, and behavioral changes in social situations. The increase in estrogen also helps shape gut and vaginal microbiota composition, which offers many local and systemic health benefits, including supporting the vaginal ecosystem in preventing dysbiosis and infections and laying the foundation for immune and neurological maturation.[11]

Pregnancy and postpartum. Pregnant women illustrate a clear connection between hormones and the microbiome, as changes in the gut microbiota during pregnancy are linked to heightened immune defenses that protect both the mother and the baby. High plasma progesterone concentrations inversely correlate with the concentration of lipopolysaccharides, inflammatory metabolites from gram-negative bacteria; this indicates that increases in these steroid sex hormones not only modulate microbiome composition but also benefit gut mucosal integrity by preventing microbial translocation.[14]

However, changes in microbial composition during pregnancy are also associated with a low-grade inflammatory state and susceptibility to blood sugar imbalances.[11] Increases in progesterone and estrogen affect how the body responds to oral bacterial plaque, leading to a higher occurrence of gingivitis and periodontitis.[19] After pregnancy, there is a very quick drop in estrogen and progesterone, which contributes to postpartum depression and intense mood changes, as well as hair loss and issues with concentration and memory.

Menopause. Postmenopause is characterized by the ceasing of the menstrual cycle and a drastic drop in estrogen and progesterone due to ovarian failure. This change poses higher risks for osteoporosis, cardiovascular disease, and vaginal dryness and increased susceptibility to urinary tract infections, as these protective hormones, particularly estrogens, plummet to sometimes close to undetectable levels.

Interestingly, a few studies have found that the gut microbiomes of postmenopausal women more closely resemble that of their male counterparts of the same age.[14] In the Study of Women's Health Across the Nation (SWAN), postmenopausal women had significantly higher plasma concentrations of intestinal fatty acid binding protein (a marker of gut epithelial cell function), lipopolysaccharide-binding protein (a marker of microbial translocation), and soluble CD14 (a marker of immune activation related to microbial translocation) compared with premenopausal women.[14]

Although more research is needed, these findings demonstrate increased gut permeability and microbial translocation related to sex hormonal changes during menopause transition. This increased gut permeability ultimately leads to higher systemic inflammatory levels and may be a driving factor for the increased health risks women face during this stage of life.

Menopause, the microbiome, and bone health. Another SWAN study showed that higher levels of inflammation (as measured by high-sensitivity C-reactive protein) were associated with lower bone mineral density and hip strength and a higher risk of fractures.[20] Women are 4 times more likely to have osteopenia than are men, with 54% of postmenopausal American women being osteopenic and an additional 30% osteoporotic. By age 80, this trend shifts as 27% of women are osteopenic and 70% osteoporotic.[21]

Besides the factors of age, a decline in estrogen, and an increase in overall systemic inflammation, microbial composition also contributes to bone loss via the gut-bone axis. There are several proposed mechanisms by which the gut microbiome interacts with bone. These mechanisms include nutrient and mineral absorption, inflammation modulation, hormone regulation (estrobolome), and microbial metabolite production. A dysbiotic state can interfere with all of these mechanisms. In particular, chronic inflammation has been shown to stimulate osteoclasts that break down bone.[22] Women with inflammatory bowel disease, for example, face increased risks of osteopenia (22%-77% of patients) and osteoporosis (17%-41% of patients) due to the inflammatory nature of the disease.[22]

Menopause, metabolic syndrome, and cardiovascular disease. Women, especially postmenopausal women, also have an increased risk for cardiovascular disease compared with men, with ischemic heart disease being the leading cause of death in women.[23] Menopause is a significant risk factor, specific to females, for developing cardiovascular disease. Menopause is linked to adverse lipid changes that contribute to atherosclerosis, as well as to weight gain and metabolic syndrome caused by impaired glucose metabolism and blood pressure regulation. Additionally, menopause leads to increased deposition of epicardial and pericardial fat.[23]

Diabetes and obesity are well-known risk factors for developing cardiovascular disease, and both are more prevalent among women—especially women of postmenopausal age. Women with diabetes have a 5-fold higher risk of heart failure than women without diabetes. A 2013 National Health and Nutrition Examination Survey showed that, of the adult population surveyed, 40% of women were considered obese compared with 35% of men.[23]

Additionally, the Framingham Heart Study found that obesity increases the likelihood of coronary artery disease by 64% in women compared with 46% in men.[23,24] All of these risk factors come back to estrogen-influencing lipid coagulation, fibrinolytic

activity, antioxidant systems, and production of vasodilatory molecules such as nitric oxide and prostaglandins.[25] Lower estrogen levels, higher inflammatory states, and susceptibility to gut dysbiosis are leading factors that put postmenopausal women at a higher risk for developing these conditions.

The vaginal microbiome

Although the gut microbiome gets the most attention of the microbiomes (given that it is the body's largest and most diverse microbial ecosystem), the vaginal microbiome plays an equally important role in women's health—especially when it comes to vaginal and urogenital health and fertility. With over 500 different bacterial species, the vaginal microbiome's composition varies among ethnicities.[26] However, the majority of the vaginal microbiomes of all ethnicities are dominated by the keystone species *Lactobacillus*.[27]

Lactobacilli and other bacteria and vaginal epithelial cells produce lactic acid, which acidifies the vagina to a pH of approximately 3.5-4.5. This acidic pH protects the vaginal microbiome from dysbiosis and resulting infections. These infections include bacterial vaginosis—the most common vaginal infection—as well as vaginal candidiasis, sexually transmitted diseases, and urinary tract infections.[27]

Lactic acid prevents the growth of pathogenic organisms and can also stimulate innate immune responses, leading to a more robust and effective response to invaders.[28] Besides releasing lactic acid, lactobacilli also produce antimicrobial compounds such as bacteriocins and hydrogen peroxide. Although there is a positive association between a healthy vaginal ecosystem and a high level of *Lactobacillus* species, it is worth noting that there is a proportion of women who have significantly low numbers of *Lactobacillus* species but are otherwise healthy and asymptomatic and yet harbor a diverse array of facultative and strictly anaerobic microorganisms.[29]

Vaginal microbiome and hormones. Differences in microbial species composition may explain why certain vaginal microbe communities seem to be more susceptible than others to external factors. For example, the vaginal microbiome may be disturbed by sexual activity and douching; by the use of antibiotics, hormonal contraceptives, and vaginal lubricants; and by the host's innate and adaptive immune systems.[27]

The stability of the vaginal microbiome also changes in response to hormone changes. In a longitudinal study of 32 healthy reproductive-age women sampled twice weekly over 16 weeks, researchers found the most stable vaginal ecosystem occurred when estrogen and progesterone levels were at their highest during the menstrual cycle; the lowest stability occurred during menses.[30] Hormones influence the pH of the vagina, which explains why women may be more susceptible to vaginal dysbiosis at specific points in their menstrual cycle.

Vaginal microbiome and estrogen. Estrogen supports the vaginal milieu and structure. It helps maintain an acidic pH in the vagina by allowing vaginal epithelial cells to accumulate glycogen, which supports the growth and adherence of beneficial bacteria like *Lactobacillus*, allowing *Lactobacillus* to produce lactic acid.[17] Estrogen also influences vaginal tissue thickness, elasticity, and lubrication. A lower estrogen level can alter the vaginal pH, disrupting the balance of the vaginal microbiome and contributing to vaginal and urinary tract atrophy and dryness—all of which lead to increased risk for infections. For this reason, perimenopausal and postmenopausal women are more susceptible to vaginal dysbiosis, urinary tract infections, pelvic floor dysfunction, urinary incontinence, prolapse, vulvodynia, dyspareunia, and sexual dysfunction.

Therapeutics involving hormone replacement therapy have been seen to restore *Lactobacilli*-dominant states and—along with other interventions such as pelvic floor therapy, lubricants, and personalized support—reduce menopausal symptoms and improve quality of life.

Vaginal microbiome and fertility. *Lactobacillus* also plays a vital role in vaginal health when it comes to fertility. As estrogen concentrations rise during pregnancy, *Lactobacillus* species, particularly *Lactobacillus crispatus*, dominate as microbiome richness and diversity decrease.[31] This increase in estrogen and *Lactobacillus* is protective against pathogenic microbes known to be associated with infertility, such as *Chlamydia trachomatis*, *Gardnerella vaginalis*, *Ureaplasma* species, and other gram-negative bacteria.[32] In one study, bacterial vaginosis, whether symptomatic or asymptomatic, was found in 28% of infertile women who also had a lower abundance of *Lactobacillus*.[32]

Vaginal microbiome health is not only critical for successful fertility but also supports gestational length and can reduce the risk of preterm birth. In the third trimester, the vaginal ecosystem reverts to a state of prepregnancy with more diversity. It is suspected that this shift is a trigger for labor, as it allows for the transfer of microbial richness to the newborn during birth, ultimately shaping the infant's immune system and neurodevelopment.[32]

CONCLUSION

The ever-fluctuating natures of hormones and the microbiome are intimately linked. Factors that influence one are sure to impose changes on the other. As more studies focus on the health differences between sexes, our understanding of the causal relationships between sex hormones, microbial balance, and immune reactions is increased. This insight should guide practitioners in taking a functional approach when considering therapeutic strategies to best support the health of female and male patients.

For example, the use of probiotics has been shown repeatedly to improve outcomes in those with digestive disorders and vaginal dysbiosis and often results in upstream improvements in systemic inflammation and immune dysfunction. Botanical medicine can offer additional health benefits, as it provides multiple beneficial mechanisms of action, including broad-spectrum antimicrobial activity, immune modulation, and anti-inflammatory effects.

Additionally, hormone replacement therapy has been clinically studied and shown to support women transitioning

into menopause by reducing atherosclerosis levels back to the low levels in perimenopause[25]; reducing vasomotor and genitourinary symptoms such as hot flashes, vaginal dryness, incontinence, and prolapse; and supporting bone mineral density, energy, mood, and quality of life.[23]

In light of today's chronic health challenges, we may all benefit from giving closer consideration to individual factors such as biological sex and life stages to best support our patients.

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